ON THE RESOLUTION OF CHLORONITROSO COMPOUNDS.

T H E S I S

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by

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C O N T E N T S.

Introduction: Historical and Theoretical.

When a ray of plane polarised light passes through a transparent optically active medium, it gives rise to two circularly polarised rays, one right-handed and the other left-handed, possessing the same amplitude, but travelling with different velocities. A phase difference is set up between the two circular components as the ray traverses the medium, and the resultant ray has its plane of polarisation rotated through an angle. This explanation of optical activity was first propounded by Fresnel[1]. The specific rotation is found to vary with the wave length, the variation being known as rotatory dispersion. When the rotation increases with decreasing wave length, the rotatory dispersion is said to be normal.

Biot[2], who first discovered that organic substances, both in the liquid state and in solution, possessed optical rotatory power, showed that for many of them, the rotation α for wave length λ was approximately proportional to $1/\lambda^2$, but there were some exceptions to this rule. It was later found that when $1/\alpha$ is plotted against λ^2, there is frequently a linear relationship between the two quantities. The straight line, however, does not pass through the origin at $\lambda^2 = 0$, but intersects the axis of zero rotation at some finite distance from the origin where $\lambda^2 = \lambda_0^2$. The rotation would therefore be better represented by the equation, $\alpha = \frac{k}{\lambda^2-\lambda_0^2}$ where k and λ_0

are constants. Thus when α is plotted against λ, the rotation tends to infinity at a characteristic wave length. It was not until 1898 that Drude[3] expressed this law in the form of a general equation,

$$\alpha = \sum \frac{k}{\lambda^2 - \lambda_0^2}$$

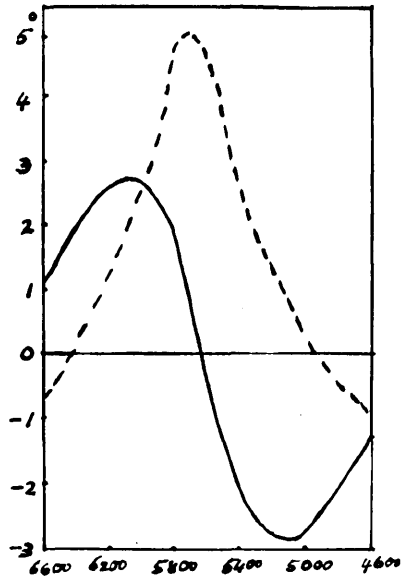
and he identified λ_0 as the wave length of the head of the absorption band. Some time later Lowry and his co-workers[4] showed that Drude's equation could be used in its simplest form (i.e. with one term) to represent the rotatory dispersion of a large number of organic compounds (including many alcohols resolved by Pickard and Kenyon[5]) but in some cases (e.g., ethyl tartrate[6]), it was necessary to employ a Drude equation with two terms of opposite sign.

In the region of an absorption band, however, the Drude equation utterly failed to represent the form of the rotatory dispersion curve. Cotton[7], who in 1896 had examined the rotatory dispersion of some coloured tartrate solutions which have absorption bands in the visible region of the spectrum, found that the rotation reached a maximum on one side of the band, and then fell through zero at the head of the band to a minimum on the other side. He also discovered that in the region of absorption, the two circularly polarised rays were absorbed to different extents by the medium, the resultant ray being elliptically polarised. This phenomenon is known as circular dichroism, and was later represented by the quantity

$\epsilon_l - \epsilon_r$ where ϵ_l and ϵ_r are the molecular extinction coefficients for left-handed and right-handed light. It can be readily shown[8] that $\epsilon_l - \epsilon_r$ is related to the measurable ellipticity τ (in radians), by the expression,

$$\tau = \frac{(\epsilon_l - \epsilon_r)\, tc}{4 \times .4343}$$

where t is the length of the layer of solution, and c is the concentration in gm.mols./litre. Cotton observed that the ellipticity varied with the wave length rising to a maximum at the head of the band. His results for potassium chromium tartrate are shown in the figure. This variation of rotation and ellipticity within an absorption band has been called the Cotton Effect.



Wave Length Å.U.
——— Rotations ---- Ellipticities.

The form of the rotatory dispersion curve within an absorbing region is very similar to that of the refractive dispersion curve. It would therefore appear that a close relationship is likely to exist between the absorption of ordinary light and that of right-handed and left-handed circularly polarised light. Moreover it is to be expected that rotatory dispersion bears a similar relationship to circular

dichroism as refractive dispersion to the absorption of unpolarised light. We will therefore consider some forms of absorption and circular dichroism curves of optically active compounds, since these are the basis of the more complex equations which are now used to represent rotatory dispersion.

Mathematical Representation of Absorption and Circular Dichroism Curves.

Helmholtz[9], assuming that absorption was due to a damping by friction between atomic vibrators, deduced an equation which was later modified by Ketteler[10] to the form,

$$\epsilon = \frac{\text{Constant} \times \lambda^2}{(\lambda^2 - \lambda_0^2)^2 + \Gamma^2 \lambda^2}$$

where ϵ is the molecular extinction coefficient, λ_0 the wavelength of maximum absorption, and Γ a damping factor.

Bielecki and Henri[11] applied this equation to a number of experimental absorption curves, and showed that there was only close agreement between the theoretical and experimental curves for a limited range of wave lengths near the centre of an absorption band. They pointed out that an absorption curve could be better represented by the empirical equation,

$$\epsilon = A\, \nu^{-\beta(\nu_0 - \nu)^2}$$

where ν_0 is the frequency of maximum absorption ϵ_0, $A = \frac{\epsilon_0}{\nu_0}$ and β is a constant embodying the half width of the band.

A similar relationship was employed by Kuhn and Braun[12],

$$\epsilon = \epsilon_0\, e^{-\left(\frac{\nu_0 - \nu}{\theta}\right)^2}$$

where θ is a parameter and can be obtained from the frequency interval ν' between the points at which ϵ is half ϵ_0 by means of the equation $\nu' = 1.6651\theta$. They showed that this equation represented their experimental curves much more accurately than the Ketteler-Helmholtz equation. Absorption curves calculated from Kuhn and Braun's equation are symmetrical on a scale of frequencies, but on a scale of wave lengths they are found to be steeper on the short wave side of the band. Now it is well known that absorption curves of chemical molecules are invariably either symmetrical on a wave length scale or steeper on the long wave side of the band. Lowry and Hudson[13] therefore used the equation,

$$\epsilon = \epsilon_0 e^{-\left(\frac{\lambda - \lambda_0}{\theta}\right)^2}$$

which has been applied successfully to compounds containing the chromophoric groups $>C = O$ and $>C = S$. A comparison of the results obtained by employing all the above equations in the fitting of the first absorption band of a number of xanthates is given in a paper by Lowry and Hudson[13].

Circular Dichroism.

Natanson[14] deduced the following equation for the form of a circular dichroism curve, which is similar to that derived

$$\epsilon_2 - \epsilon_1 = \frac{\text{Constant} \times \lambda}{(\lambda^2 - \lambda_0^2)^2 + r^2\lambda^2}$$

by Ketteler and Helmholtz for the absorption, and differs only by a factor of $1/\lambda$. By dividing one by the other it can be

seen that the ratio $\frac{\epsilon_l - \epsilon_r}{\epsilon}$ in an absorption band is proportional to the frequency. (This ratio is represented by "g" and is known as the anisotropy factor.) A series of equations can therefore be deduced for circular dichroism corresponding to the absorption equations previously mentioned.

The absorption equation of Kuhn and Braun leads to an equation for circular dichroism of the form,

$$(\epsilon_l - \epsilon_r) = (\epsilon_l - \epsilon_r)_0 \frac{\nu}{\nu_0} e^{-\left(\frac{\nu_0 - \nu}{\theta}\right)^2}$$

where ν_0 is the frequency of maximum circular dichroism $(\epsilon_l - \epsilon_r)_0$. In the case of potassium chromium tartrate, Kuhn and Szabo omitted the factor $\frac{\nu}{\nu_0}$ thereby obtaining better results.

Lowry and Hudson's absorption equation gives, for circular dichroism, the equation,

$$(\epsilon_l - \epsilon_r) = (\epsilon_l - \epsilon_r)_0 \frac{\lambda_0}{\lambda} e^{-\left(\frac{\lambda - \lambda_0}{\theta}\right)^2}$$

Analysis of Rotatory Dispersion in Regions of Absorption.

In order to account for the anomalous form of the rotatory dispersion curve in the region of absorption, Drude extended his original equation by introducing a friction coefficient, but although he was able to account for the phenomenon of circular dichroism, his expression for rotatory dispersion was not given in a convenient form.

Natanson[14] with the help of a damping factor arrived at the equation for rotation,

$$\alpha = \frac{D(\lambda^2 - \lambda_0^2)}{(\lambda^2 - \lambda_0^2)^2 + \Gamma^2\lambda^2}$$

His corresponding equation for circular dichroism has already been mentioned. The damping factor Γ is numerically equal to the half width of the circular dichroism band, and $D = \Gamma \times (\epsilon_l - \epsilon_r)_0$ where $(\epsilon_l - \epsilon_r)_0$ is the maximum value of the circular dichroism. Natanson used his equation to calculate the rotatory dispersion of potassium chromium tartrate from Cotton's measurements of the circular dichroism, and obtained a curve which agreed fairly well with Cotton's experimental curve. It has been mentioned previously, however, that the Ketteler-Helmholtz equation, which incorporates the damping factor Γ, was inadequate to express the absorption curves of many compounds satisfactorily. It therefore follows that the equations for circular dichroism and rotatory dispersion in the region of absorption must be modified in the same way as the absorption equation.

Kuhn and Braun[12], by working out a special case of Born's[15] theory of coupled electronic vibrators, arrived at an expression which, when integrated over the absorption band, gave the result

$$[M] = \frac{100}{2\sqrt{\pi}} \frac{(\epsilon_l - \epsilon_r)_0}{\log_{10} e} \frac{\nu}{\nu_0} \left[e^{-\left(\frac{\nu_0 - \nu}{\theta}\right)^2} \int_0^{\frac{\nu_0 - \nu}{\theta}} e^{x^2} dx - \frac{\theta}{2(\nu_0 + \nu)} \right]$$

where $[M]$ is the molecular partial rotation associated with the absorption band, ν_0 is the frequency of the maximum value of circular dichroism, $(\epsilon_l - \epsilon_r)_0$, and θ is a parameter embodying

the half width of the circular dichroism. When the latter data are not available, the above equation may be applied by assigning an arbitrary value to $(\epsilon_\ell - \epsilon_r)_0$ and employing the values of ν_0 and θ given by absorption data. In the case of the dimethylamide of α-azidopropionic acid, for which no circular dichroism measurements were made (until a later date) Kuhn[12] used the absorption data in applying the above equation to calculate the partial rotations due to the absorption band. The resultant curve obtained by subtracting the partial rotations from the observed, showed no anomaly due to the azido group. This equation has also been used by Kuhn and co-workers[16] to calculate the partial rotations in molecules containing the groups ONO, Ph, Cl, Br, and I. In 1937 Tsuchida[17] employed a modification of this equation to analyse the circular dichroism and rotatory dispersion curves of ammonium-α-bromocamphor-π-sulphonate. More recently, Kuhn's equation has been made use of by Kar[18] in the analysis of the circular dichroism and rotatory dispersion curves of ammonium vanadyl d-tartrate, fairly good agreement being obtained with the former but in the latter case the results were not so satisfactory.

Lowry and Hudson[13] using wave-lengths instead of frequencies, developed the following equation for rotatory dispersion on exactly the same lines as Kuhn and Braun,

$$[M] = \frac{100}{2\sqrt{\pi}} \frac{(\epsilon_\ell - \epsilon_r)_0}{\log_{10} e} \frac{\lambda_0}{\lambda} \left[e^{-\left(\frac{\lambda-\lambda_0}{\theta}\right)^2} \int_0^{\frac{\lambda-\lambda_0}{\theta}} e^{x^2} dx + \frac{\theta}{2(\lambda+\lambda_0)} \right]$$

This equation has been applied by Lowry and Hudson to calculate the partial rotations in the region of absorption of a considerable number of compounds. In some cases (e.g. the xanthates[13]), fairly good results have been obtained, while in others the residual curves crossed the zero axis at several points. (See Lowry's, "Optical Rotatory Power", ch.XXXIV.) Results for compounds containing the CHO and CO groups, obtained by Hudson, Wolfrom and Lowry[19] and later by Lowry, Simpson and Allsop[20], were not too satisfactory. Mathieu and Royanette[21] found fairly good agreement between the calculated and observed circular dichroism and rotatory dispersion curves of cyanocamphor. Particularly striking results were obtained by Mitchell and Simpson[22] when employing this equation to calculate the partial rotations due to the NO group in l-menthyl d-β-chloro-β-nitrosobutyrate, the resultant curve being entirely free from anomalies. In Part II of this thesis, an application of the same equation to another nitroso compound is described, and again a fairly smooth resultant curve was obtained.

A number of other equations have been put forward based on later theories of optical activity. With the replacement of the classical interpretation by the quantum mechanical treatment of dispersion, it became necessary to revise the existing theories. Born's classical theory of coupled vibrators, already referred to in connection with Kuhn's equation, was 'translated' into quantum mechanical language by

Rosenfield[23], and Born and Jordan[24], but the results were unsuitable for practical application. In 1935 Born[25] attempted to simplify his earlier classical theory for practical purposes, but it still remained too complicated to be of more than limited use. In 1937 Kirkwood[26], on the basis of Rosenfield's results, derived a quantum theory of optical activity which was applied with some success in one or two cases. About the same time Condon, Altar and Eyring[27] (and later Kauzmann, Walter and Eyring[28]), showed on the basis of quantum mechanics, that not only the coupling of vibrating electrons, but also the motion of a single electron can give rise to optical activity. Their theory was successfully applied to the case of methyl phenyl carbinol nitrite, where the calculated contribution of the nitrite group to the optical rotatory power of the molecule agreed fairly well with the experimental results.

Unfortunately, none of these theories gives a completely satisfactory explanation of optical activity, and most of the theoretical relationships deduced are too involved for application to experimental data. For practical purposes the relationship formulated by Kuhn has proved the most convenient.

Asymmetric Photochemical Action.

We have seen that the phenomenon of circular dichroism arises from the unequal absorption of the two forms of circularly polarised light by an optically active isomer. It follows that the two isomers (in a racemic mixture) will

absorb one form of the light to different extents. If, moreover, absorption of the light in the region of a circularly dichroic absorption band brings about photochemical decomposition, then the irradiation of a racemic mixture with one form of circularly polarised light of suitable wave length should result in the preferential decomposition of one isomer leaving an excess of the other. Thus the originally inactive solution should become optically active. Such a process is known as asymmetric photolysis, and the idea was originally suggested by van't Hoff[29] in 1894. Cotton regarded the possibility of producing optical activity in this way as a corollary to his discovery of circular dichroism.

It is essential that the chemical decomposition should be brought about at those wave-lengths at which the active isomer exhibits circular dichroism. Cotton[30] attempted the asymmetric photolysis of a solution of copper d-tartrate, which showed circular dichroism at the red end of the spectrum and was decomposed by sunlight. After irradiating solutions with right and left-handed circularly polarised sunlight until the decomposition was well advanced, no signs of rotation were observed. This, as was later shown by Byk[31], was because the solution was not decomposed by red light as Cotton had supposed, but by ultraviolet rays (3500-4000 A). Mitchell[32] showed that no circular dichroism was exhibited by the solution in the ultraviolet region of the spectrum.

Although in theory the idea of asymmetric photolysis is a very attractive one, its experimental realisation is a matter of great difficulty. In the first place, although many substances are known to exhibit circular dichroism, the relative difference in the absorption of the two kinds of light is usually very small. This difference is expressed as the anisotropy factor $g = \frac{\epsilon_l - \epsilon_r}{\epsilon}$, (to which reference has already been made). In order for measurable rotations to be produced, both g and the specific rotation of the active isomer should be as large as possible. Kuhn[8], assuming that Einstein's law of photochemical equivalence[33] holds for a compound, derived a formula which may be used to predict the value of rotation developed by the asymmetric photolysis of a racemic mixture of the compound. He calculated that

$$\alpha' = \alpha \, g/2 \, (1-\beta) \log \frac{1}{1-\beta}$$

where α' = rotation developed from a solution of the d.l-mixture,

α = rotation for solution of pure d or l-compound (conc. equal to that of d.l-mixture at start),

g = anisotropy factor,

β = degree of decomposition.

According to this equation, Kuhn calculated that the maximum rotation will be obtained at about 60% decomposition. (Renaud[34] has recently made some calculations relative to asymmetric decompositions, and has shown that appreciable rotations should be obtained by starting with large quantities

of material and decomposing it as far as is practicable, i.e., until sufficient of the unchanged substance can be recovered to fill the polarimeter tube. This fact, however, had already been realised by investigators in this field.)

In addition to the conditions mentioned above, there are three photochemical requirements:- 1) A quantum efficiency of approximately unity. 2) Absence of dark reactions. 3) Destruction by the light of the asymmetric centre producing the Cotton effect.

Many attempts have been made by various workers to bring about asymmetric photochemical decomposition, most of them being unsuccessful. A number of these are described in Mitchell's "Cotton Effect and Related Phenomena", London, 1933, p.60.

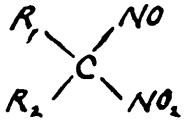
The first successful attempt was carried out by Kuhn and Braun[35] with ethyl α-bromopropionate using circularly polarised ultraviolet light, but the rotation in this case was only of the order of 0.05°. More encouraging results were obtained in 1930 when Kuhn and Knopf[36] decomposed the dimethylamide of α-azidopropionic acid again with circularly polarised ultraviolet light. Examination of the circular dichroism of the optically active isomer, gave a value of 0.024 for the anisotropy factor. After 37% decomposition with left-handed light, the unchanged compound was recovered and gave a rotation of -1.04°. The corresponding experiment with right-handed light after 35% decomposition gave a reading of $+0.78^{\circ}$.

About this time Mitchell[37] examined the rotatory dispersion and circular dichroism of caryophyllene nitrosite and discovered a Cotton effect due to the nitroso group in the red region of the spectrum. The anisotropy factor of this compound was as high as 0.12, and was therefore considered to be very suitable for asymmetric photochemical work. Since the racemic form of caryophyllene is not known, the nitrosite of the analagous compound, humulene, was tried for the asymmetric decompositions[32]. After irradiation with circularly polarised red light until 65% decomposition, rotations of +0.3° and -0.3° were obtained using mercury yellow light.

Since these last two very successful experiments, one or two asymmetric syntheses have been reported. Karuginis and Drikos[38] in 1934 chlorinated a triarylmethyl radical under the influence of circularly polarised light, and obtained a product with a maximum rotation of 0.15°. In 1945 Davis and Ackerman[39] claimed an asymmetric synthesis of ethyl d-tartrate from ethyl fumarate and hydrogen peroxide in the presence of circularly polarised light. In this case the rotation was only 0.073°. Three other asymmetric photochemical experiments have been recorded by Davis and Heggie[40], Betti and Lucchi[41], and Ghosh[42], but the rotations in these cases were again very small.

As a result of the successful attempt by Mitchell with humulene nitrosite, it was thought desirable to extend this work to simpler nitroso compounds.

The nitrosites of bornylene, phellandrene, and zingibrene, were studied by Mitchell and Cormack[43]. These were white solids which gave colourless solutions in organic solvents, the solute being dissolved in the bimolecular form. A solution of bornylene nitrosite in toluene turned blue on warming owing to the dissociation of the double molecules, but became colourless again on cooling. The colourless solution at ordinary temperatures showed normal rotatory dispersion, but on warming, the blue solution obtained exhibited circular dichroism and had an anisotropy factor of 0.04. Owing to considerable decomposition taking place as a result of prolonged heating which would have been necessary for photochemical experiments, further work on the compound was abandoned. The nitrosites of phellandrene and zingibrene were even less stable. Carson[44] investigated α-pinene nitrosochloride and bis nitroso-l-menthone, but these also were found to be too unstable for photochemical work.

Some pseudo-nitroles of the type  were next examined. These compounds, although white in the solid state, dissolved in organic solvents to give blue solutions which absorbed oxygen under the influence of red light to give the corresponding dinitro compounds. If R_1 and R_2 are different alkyl radicals, it can be seen that this photochemical reaction results in the destruction of the asymmetric centre. Unfortunately, Mitchell and Gordon[45] found that the photo-oxidation was accompanied by a considerable dark

reaction so no further work was carried out with these substances.

Attention was then directed to chloronitroso compounds as a result of experiments carried out by Mitchell and Carson[46] on the photochemical action of nitrosyl chloride on n-hexane. They obtained a mixture of β-chloro-β-nitroso and γ-chloro-γ-nitroso-hexane. A solution of this mixture in methyl alcohol, when exposed to red light in sealed tubes, gradually lost its blue colour, oxime hydrochlorides being produced. This result was important because it indicated that the asymmetric centre had been destroyed by the light, and these compounds might therefore be suitable for asymmetric photochemical work. Rheinboldt and Dewald[47], who prepared a number of simple nitroso compounds of the type,

$$R_1 - \underset{\underset{Cl}{|}}{\overset{\overset{NO}{|}}{C}} - R_2$$

(where R_1 and R_2 are alkyl radicals), had found that exposure of solutions of these substances to light in the presence of air brought about photochemical oxidation to the corresponding chloronitro compounds. Measurements of the quantum efficiency γ for the photochemical decomposition by red light of some chloronitroso compounds were made by Hammick and Lister[48] but steps were not taken to exclude oxygen from the reaction vessels and high values for γ were obtained. Later, Mitchell and Cameron[49] studied the photolysis of β-chloro-β-nitrosobutane in the absence of oxygen and found γ to be 1.2. They also

made a very thorough investigation of the decomposition products.

It now remained to be shown that this type of compound exhibited the Cotton effect in the region of absorption, and in order to determine this, it was necessary to obtain a chloronitroso compound optically active. This was successfully accomplished by Mitchell and Simpson[22] who resolved l-menthyl β-chloro-β-nitrosobutyrate, which exhibited circular dichroism in the red region of the spectrum and had an anisotropy factor of 0.038 (in ethyl alcohol). By analysis of the rotatory dispersion curve of the above compound, the authors showed that the contribution due to the nitroso group was not influenced by the presence of the chlorine atom.

All the above data collected for chloronitroso compounds appeared to indicate their suitability for asymmetric photochemical work. That this was in fact the case, was verified when Mitchell and Dawson[50] obtained positive results with β-chloro-β-nitroso-α-δ-diphenylbutane.

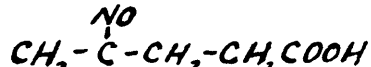
The purpose of the present research was to extend the above work on chloronitroso compounds. In Part I of this thesis two successful asymmetric photochemical experiments are described. As the magnitudes of the rotations produced were different in the two cases, it was thought desirable to resolve some more chloronitroso compounds in order to measure and compare their

anisotropy factors. Such knowledge would enable one to predict the type of compound which would give the best results. Part II of this thesis is therefore concerned with the problem of resolving chloronitroso acids, since acids are the most suitable type of chloronitroso compound for resolution purposes. In this section the first resolution of a chloronitroso acid is described.

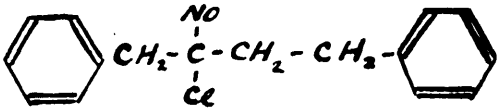
Part I.

The Partial Resolution of Chloronitroso Compounds by Asymmetric Photolysis.

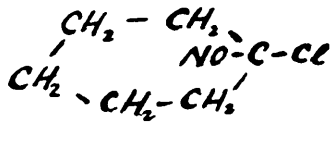
The photochemistry of the chloronitroso compounds I - IV has been investigated by Mitchell, Schwarzwald and Simpson[51].



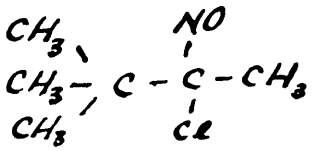
γ-chloro-γ-nitroso-valeric acid
I



β-chloro-β-nitroso-αδ-diphenylbutane
II



1-chloro-1-nitroso-cyclohexane
III



β-chloro-β-nitroso-γγ-dimethylbutane
IV

Quantum efficiency data for all four compounds are given and the decomposition products of I and II in methyl alcohol are also described. Of these four compounds, III is unsuitable for asymmetric photochemical work as there is no asymmetric carbon atom in the molecule, while I undergoes esterification during photolysis and so would also be unsuitable. The compound II was selected for further work by Mitchell and Dawson[50], as it fulfilled the three photochemical requirements mentioned previously:- a) The quantum efficiencies for λ 6100 and 6580 A were 1.10 and 0.78 respectively, giving an average of 0.94. b) There was no dark reaction. c) The main product of photolysis in methyl alcohol was the hydrochloride of α-δ-diphenylbutan-β-one-oxime, showing that the asymmetric centre had been destroyed by the light. In addition, the compound was a stable solid, fairly readily prepared and easily

recoverable from a partially decomposed solution.

Asymmetric photochemical experiments were therefore carried out, the irradiation with circularly polarised light being continued until 90% of the chloronitroso compound had been decomposed. As it was difficult to isolate the unchanged substance if the decomposition had gone too far, the photolysis was carried out in four stages (one of 50% and three of 40%), the unattacked material being recovered at each stage. Polarimetric examination of the final specimens which had been exposed to right-handed and left-handed light respectively gave the values $\alpha^{20°}_{5300}$ = -0.10° and +0.11° (ℓ = 1, c = 4% in methyl alcohol), or $[\alpha]^{20°}_{5300}$ = -2.50° and +2.75°. Unfortunately, at the later stages of the decomposition a green oil was produced from which it became increasingly difficult to isolate the unchanged blue substance. IV was therefore selected for asymmetric photochemical work as it was considerably more stable, and the decomposition could be carried beyond 90% without any green colour becoming perceptible.

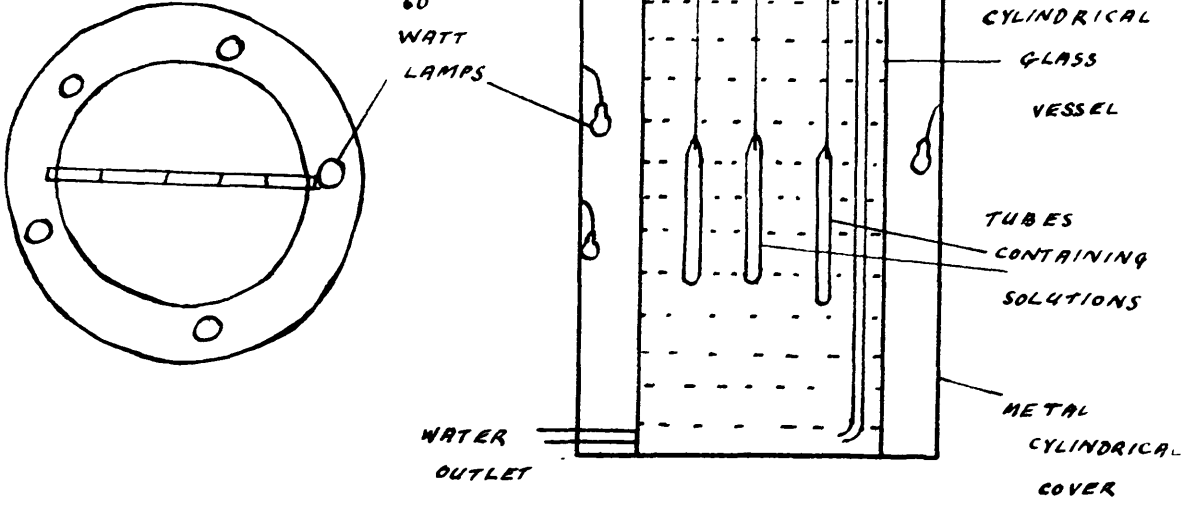
The quantum efficiencies of this compound for λ 6700 and 6140 A were found by Mitchell and his co-workers[51] to be respectively 0.62 and 0.93, giving an average value of 0.78. This, although less than unity, was sufficiently high for practical purposes, and definitely indicated that no chain reactions were occurring. Moreover, solutions of the blue compound left for many weeks in the dark showed no signs of

decomposition, so that two of the photochemical requirements were satisfied. In order to ascertain whether the asymmetry of the carbon atom was destroyed by the light, it was necessary to investigate the photochemical decomposition products.

The Photolysis of β-chloro-β-nitroso-γγ-dimethylbutane.

a). In Methyl Alcohol.

Since chloronitroso compounds in the presence of oxygen or air decompose photochemically to give the corresponding chloronitro compounds, the decompositions were carried out in sealed tubes to exclude all air, and the methyl alcohol used was previously distilled in a nitrogen atmosphere to remove dissolved oxygen. 5% solutions of the chloronitroso compound were made up, and exposed to light in sealed glass tubes in the apparatus shown.



In order to prevent the tubes from being heated by the lamps, they were kept immersed in running water. After some days the blue solutions faded, gradually becoming colourless. Whenever possible, sunlight was used as the light source, the time of exposure required being considerably less. In this case the tubes were kept cold by immersing in water to which ice was frequently added.

Examination of the decomposition products.

After complete decomposition, the tubes were opened, the solutions filtered, and the methyl alcohol removed at room temperature under reduced pressure. There remained a light brown solid which was washed well with ether in which most of it was insoluble. The ether filtrate was evaporated leaving a drop of oil, which, on standing, deposited white crystals, m.p. 159°C (with sublimation). On testing for the elements, chlorine was found to be present. Insufficient material was available for analysis purposes, but a mixed melting point with tetramethylethylene dichloride (which also melts at 159°C with sublimation) showed no depression.

An examination was then made of the solid (insoluble in ether), which constituted the main decomposition product. A small portion was readily dissolved in water, and the addition of silver nitrate solution gave a white silver chloride precipitate. Another portion was suspended in dry ether, and on passing in chlorine, a blue colour was obtained. Removal of

the ether gave a blue solid identical with the substance used in making up the original solutions. The remainder of the residue was boiled with methyl alcohol and allowed to stand when white crystals were deposited. M.P. 74°C. (Pinacolone oxime melts at 74°C.) On mixing the crystals with pinacolone oxime, no depression in the melting point was observed. The solid remaining after the evaporation of the methyl alcohol and washing with ether was therefore the oxime hydrochloride of pinacolone, and this on boiling with methyl alcohol gave the free oxime.

Estimation of hydrogen chloride liberated in the photolysis.

Owing to the volatility of the oxime hydrochloride only one third of the theoretical yield was obtained after removing the solvent. It was possible, however, by titration, to estimate the amount of hydrogen chloride formed, and if the oxime hydrochloride was the only product of photolysis, then a 100% yield of hydrogen chloride would be expected. A known weight of the chloronitroso compound in methyl alcohol was therefore decomposed, and to the colourless solution an excess of $^{N}/_{10}$ silver nitrate was added, the excess being titrated against $^{N}/_{10}$ ammonium thiocyanate using ferric alum as indicator. The yield of hydrogen chloride was found to be 84%. This result indicated that the oxime hydrochloride was the main, though not the only product. For the formation of this substance from the chloronitroso compound, two hydrogen atoms were required.

Since no evidence of double molecule formation could be found (c.f. Mitchell and Cameron[49]), a search was made for formaldehyde as this was detected by Mitchell, Schwarzwald and Simpson[51], among the decomposition products of β-chloro-β-nitroso-$\alpha\delta$-diphenylbutane, the formaldehyde coming from the methyl alcohol after it had given up two hydrogen atoms.

Search for formaldehyde.

A tube containing the decomposed solution was emptied and its contents steam distilled, the distillate being received into an aqueous solution of dimedone. No precipitate formed after two days' standing. The absence of a positive test for formaldehyde might be due to its ease of polymerisation by ultraviolet light. Ethyl alcohol was therefore used as solvent and on opening the tube the odour of acetaldehyde was distinctly perceptible. Its presence was shown qualitatively by Schiff's reaction (magenta solution, decolourised by sulphur dioxide, had its colour immediately restored by a portion of the decomposed solution). Distillation of another portion into an aqueous solution of dimedone gave, on standing, a crystalline solid, which, after crystallisation from alcohol, was shown by m.p. and mixed m.p. to be the derivative of acetaldehyde. M.P. 139°C.

In order to test for formaldehyde, the blue solution in methyl alcohol was decomposed by red light from a carbon arc running at 10 amps. The light was first passed through a circulating water filter (to cut out infra-red rays and heat

radiations) and then through a red filter to remove ultra-violet rays. After decomposition, a positive silver mirror test was obtained with the colourless solution, and a dimedone derivative identical with that of formaldehyde. To prepare this derivative, the decomposed solution was mixed with an aqueous-alcoholic dimedone solution and left to stand. The solution was then concentrated under reduced pressure and the solid derivative which separated was shown by m.p. (189°C) and mixed m.p. to be in fact the dimedone derivative of formaldehyde.

b). In Ethyl Alcohol.

Again the oxime hydrochloride of pinacolone was the main product, the two hydrogen atoms required being obtained from the solvent with the production of acetaldehyde.

c). In Carbon Tetrachloride.

Approximately 5% solutions were made up and exposed to light in sealed tubes. The time for complete decomposition was considerably longer in this case than when methyl or ethyl alcohol was used as solvent. During the course of the decomposition a continuous stream of gas bubbles was observed. In another experiment this gas was collected in a burette and identified as nitrogen. An aqueous extract of the decomposition solution was found to contain nitrous acid and traces of hydrochloric acid. After removing the solvent under reduced pressure, a white solid was obtained from the residue, soluble in ether but insoluble in water. It strongly resembled camphor in

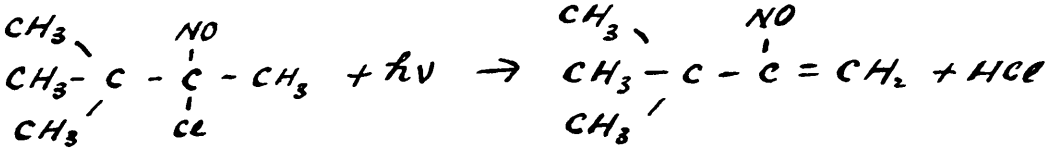
smell, and after being crystallised from methyl alcohol, melted at 159°C with sublimation. (Found: C, 46.3; H, 7.7; Cl, 45.6. Calculated for tetramethylethylene dichloride of formula $C_6H_{12}Cl_2$: C, 46.5; H, 7.7; Cl, 45.8%). The white substance was therefore tetramethylethylene dichloride. An intractable gummy material was also found to be present in the residue.

Decompositions in benzene and ether required about the same time of exposure as in carbon tetrachloride and gave the same products.

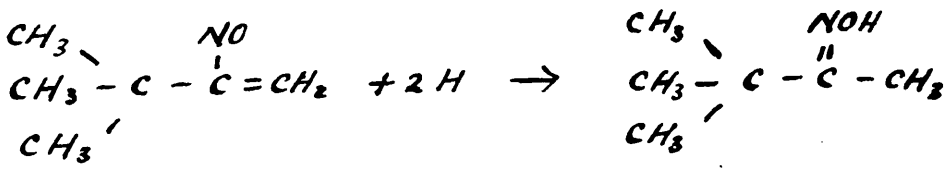
During further decompositions in methyl alcohol, the evolution of nitrogen was observed to a small extent, and traces of nitrous acid were detected among the products.

Discussion.

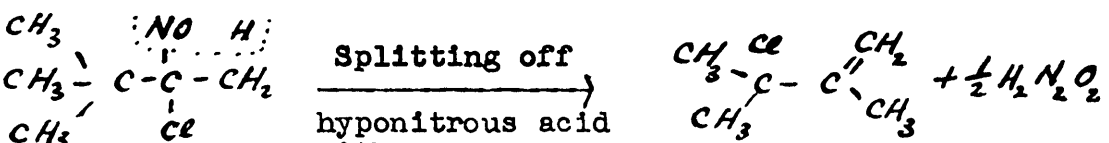
β-chloro-β-nitroso-γγ-dimethylbutane can decompose photochemically in two different ways. In methyl or ethyl alcohol, an activated molecule appears to be first produced by the absorption of one quantum of light energy by the nitroso group, and hydrogen chloride is then split off. (Cf. Mitchell, Schwarzwald and Simpson[51]).

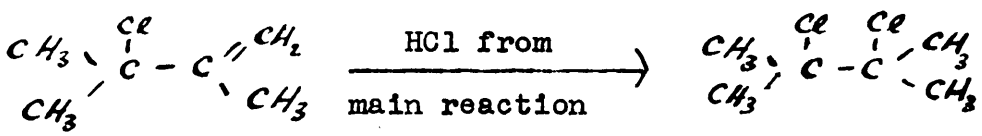


The two hydrogen atoms required to convert the unsaturated residue into the oxime of pinacolone are obtained from the solvent with the production of the corresponding aldehyde.



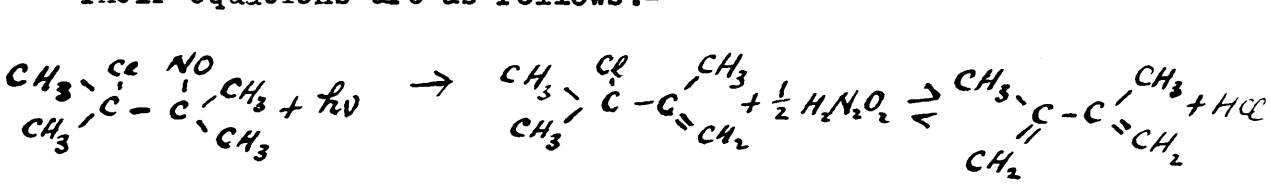
A secondary reaction also takes place to a small extent giving nitrogen, nitrous acid, and tetramethylethylene dichloride. It may be formulated thus:-

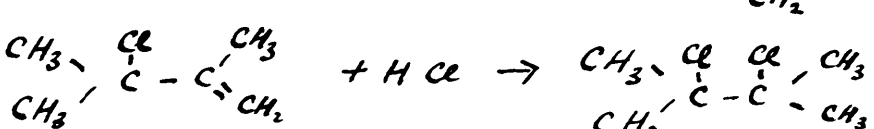




This secondary reaction explains why the percentage of hydrogen chloride obtained is lower than the theoretical value.

In solvents such as carbon tetrachloride, benzene and ether, the reaction mechanism appears to be similar to that postulated by Hammick and Lister[48] for the photochemical decomposition of tetramethylethylene nitrosochloride in benzene. Their equations are as follows:-





The only difference in the case of β-chloro-β-nitroso-γγ-dimethylbutane would appear to be that nitrous acid is split off and this is followed by a rearrangement of the molecule. The dimethylbutadiene undergoes polymerisation when exposed to light and probably forms part of the residual gummy material.

Having ascertained that the decomposition by light of the substance in methyl alcohol (as well as in other solvents) destroys the asymmetric centre, all three photochemical requirements are satisfied. In addition, the compound is a stable solid and is very easily prepared. Owing to its extreme volatility, the method used by Mitchell and Dawson[50] for the recovery of the unchanged blue compound from a partially decomposed solution was not practicable. The difficulty was overcome, however, simply by pouring the solution into water in which the oxime hydrochloride dissolved, and extracting the unchanged blue substance with ether.

Absorption Spectrum.

The absorption due to the nitroso group was examined with a Hilger Spekker photometer in conjunction with a Hilger glass spectrograph in which wave lengths from 3,600 A to 10,000 A were recorded on a 10" x 4" plate. Ilford long range plates were very suitable. A ribbon filament lamp (6 v., 16 amp.) served as light source. The absorption in benzene had been previously examined by Hammick and Lister[48], and their

results were confirmed. Data for the compound in methyl and ethyl alcohols, and benzene, are shown in Table I where ϵ represents the molecular extinction coefficient. By plotting ϵ against λ, the absorption curves for the compound were obtained and are shown in Fig.1. From the graph it is seen that the maximum value of ϵ varies with the different solvents, but with all three, the head of the band is at approximately the same wave length, viz., 6700 A.

The Asymmetric Photolysis of α-chloro-β-nitroso-$\gamma\gamma$-dimethylbutane.

Two rectangular glass cells of 50 cc. capacity were used to contain the solutions, one being exposed to right-handed and the other to left-handed circularly polarised light. The tops of the cells were fitted on with secotine and left overnight to harden. 50 ccs. of an approximately 10% solution of the chloronitroso compound in methyl alcohol were added to each cell through a small hole in the top of each, and capillaries, fitted with taps, were ground into the holes, care being taken to include no air bubbles. (The methyl alcohol had been previously distilled in a nitrogen atmosphere to remove dissolved oxygen.)

The arrangement for the photolysis is shown in the diagram.

Table I.

Absorption of β-chloro-β-nitroso-γγ-dimethylbutane.

In Methyl Alcohol c=0.09872 gm.mols/l			In Ethyl Alcohol c=0.09634 gm.mols./l		
λ		ε	λ		ε
7360		1.01	7320	5480	1.04
7220	5760	2.03	7200	5800	2.08
7160	5850	3.04	7110	6000	3.11
7090	5950	4.05	7050	6110	4.15
7020	6040	5.07	7000	6220	5.19
6970	6120	6.08	6950	6300	6.23
6930	6200	7.09	6900	6370	7.27
6880	6280	8.10	6860	6440	8.31
6840	6360	9.12	6810	6500	9.34
6810	6460	10.13	6770	6580	10.38
6780	6510	11.14	6730	6620	11.42
6750	6560	12.15	6710	6660	12.46
6720	6600	13.17			
6710	6660	14.17			

Table I (Continued)

In Benzene

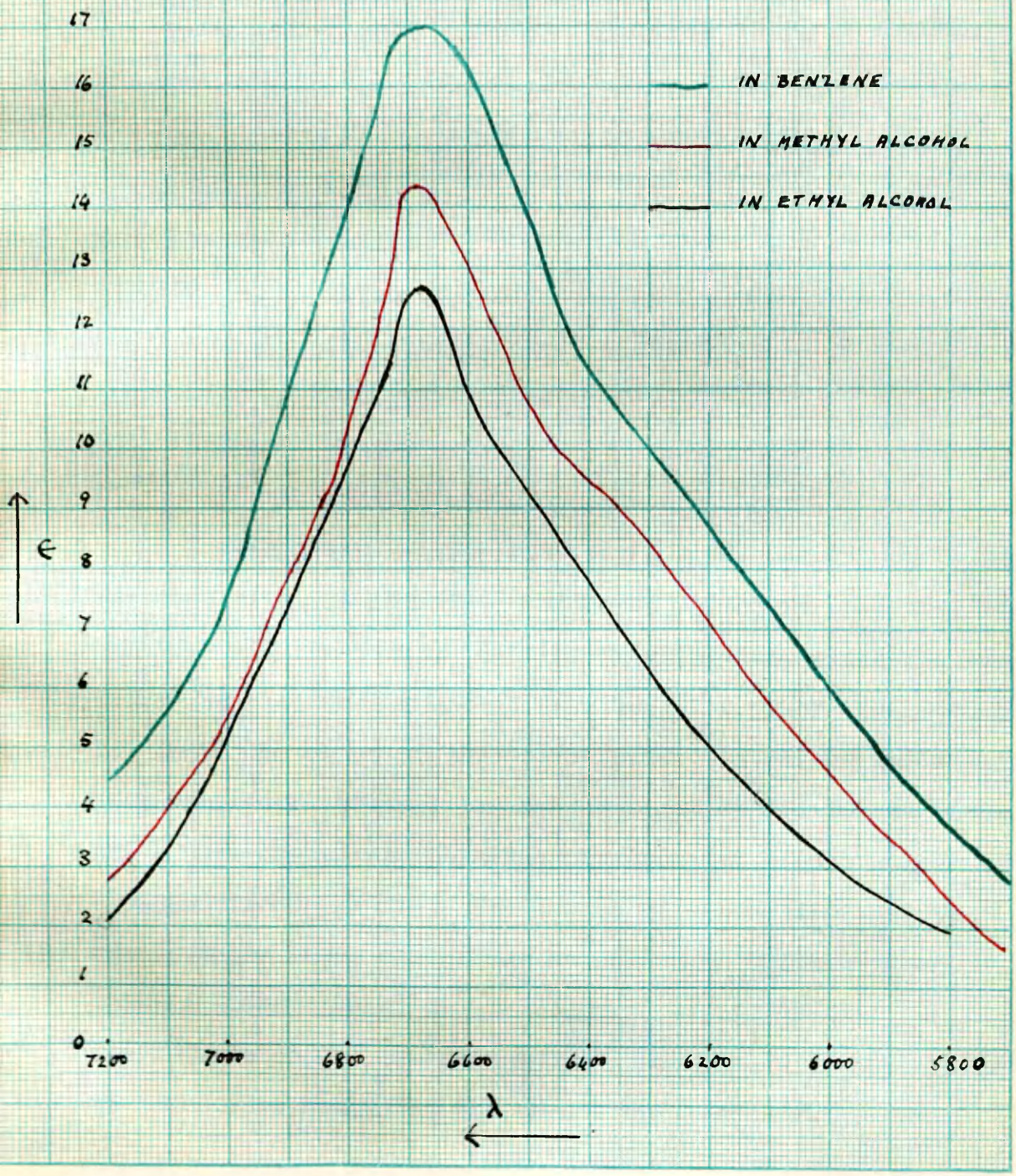
c = 0.08409 gm.mols./l

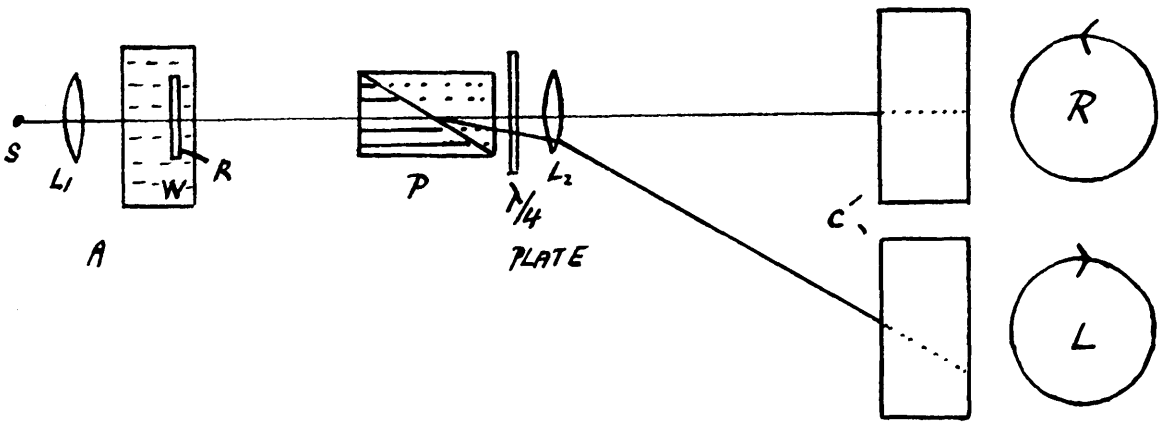
λ		ϵ
7500	5430	1.19
7350	5650	2.38
7250	5780	3.57
7160	5900	4.76
7080	5990	5.95
7010	6080	7.14
6970	6170	8.33
6940	6260	9.52
6900	6350	10.70
6860	6430	11.90
6830	6470	13.07
6790	6510	14.28
6750	6560	15.46
6730	6620	16.65

FIG. 1.

ABSORPTION

β-CHLORO-β-NITROSO-γγ-DIMETHYLBUTANE





S = Light source.

L_1, L_2 = Lenses.

A = Metal stop with square aperture 2" x 2".

W = Circulating water filter.

R = Red glass filter.

P = Rochon prism.

C = Cells containing solution.

A carbon arc (with a mechanical feed) running at 24 amps. was used as light source. The water filter trapped the infra red rays and the heat radiations from the arc, while the red filter only allowed light of wave length greater than 6000 A to pass. By means of the Rochon prism, the light was separated into two beams (plane polarised at right angles to each other) which were circularly polarised in opposite senses by passage through the $\lambda/_4$ plate. The latter was so chosen that it rendered the light circularly polarised in the region of maximum absorption of the compound.

To decompose the solutions to the extent of 60%, about 45 hours were required, the amount of decomposition being

determined by means of a photoelectric colorimeter. At this point (60% photolysis) some of the blue solution was syphoned out of each cell into two 1 dcm. polarimeter tubes to see if any rotation had been developed. With a light source of wave length 5200 A (obtained by using a 100 c.p. Pointolite lamp and a monochromator in conjunction with a polarimeter), a difference of 0.14° was observed between the two tubes.

From each of the two cells about 1.5 gms. of the unchanged blue compound were recovered in a manner previously described. The decomposition of 10% solutions to the extent of 60% was repeated twice so that almost 5 gms. of the substance were recovered to serve as the starting material for the next stage. The process was then repeated with the recovered material and after 60% decomposition, the solutions were again transferred to the polarimeter tubes. (At this stage the extent of decomposition was about 82%.) It was observed that the solution which had been exposed to right handed light gave the value $\alpha^{t°}_{5200} = -0.11°$ and that exposed to left-handed light, the value $\alpha^{t°}_{5200} = +0.10°$, or $[\alpha]^{t°}_{5200} = -2.75°$ and $+2.5°$ (c = 4% in methyl alcohol, ℓ = 1). As before, the undecomposed material was recovered.

The cells were then filled with 16% solutions and these were decomposed to about 82% (85 hours being required). A difference of 0.21° was again observed when 4% solutions of the recovered substance were examined in the polarimeter.

There was sufficient recovered material from the last two experiments to fill the cells with 4% solutions, and these were decomposed until the concentration was 1.2%. At this stage the extent of decomposition was 94%. Difficulty was experienced in the recovery of the undecomposed substance owing to the accumulation of the secondary decomposition product - tetramethylethylene dichloride. Its presence was suspected at previous stages of the decomposition, but it was only at this advanced stage that it caused any serious difficulty. More dilute solutions were used for the polarimetric readings as this secondary product was apt to crystallise out in the polarimeter tubes. The concentrations of the solutions used were measured by means of the photoelectric cell. One solution of 2% concentration gave a rotation of -0.07° or $[\alpha]_{5780}^{18^{\circ}} = -3.5^{\circ}$, while the other solution of concentration 3% gave a rotation of $+0.11^{\circ}$ or $[\alpha]_{5780}^{17^{\circ}} = +3.6^{\circ}$. Thus an increase in the specific rotation from 2.5° to 3.5° has been obtained by carrying the photolysis from 82% to 94%.

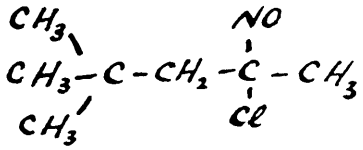
Separation of Secondary Product.

Owing to the accumulation of this secondary product, the asymmetric photolysis could not be taken further unless some efficient method of separating it from the chloronitroso compound could be devised. Attempts at a separation by extraction with, or crystallisation from, different solvents were unsuccessful owing to the ease of solubility of both substances in most organic solvents. Steam distillation proved

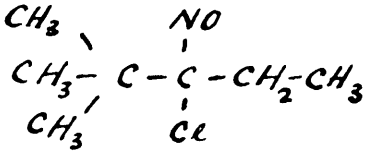
ineffective as both compounds were steam volatile and a separation by chromatographic analysis was also unsuccessful.

Investigation of other compounds.

The two compounds, β -chloro-β-nitroso- δδ -dimethylpentane, V, and γ -chloro- γ-nitroso-ββ -dimethylpentane, VI,



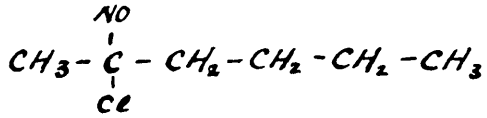
V



VI

were then prepared in order to investigate their suitability for asymmetric photochemical work. Since in each of these compounds there is a CH_2 group adjacent to the asymmetric carbon atom, it was considered that they might decompose more rapidly under the action of light than β -chloro-β-nitroso-γγ -dimethyl butane, and show less tendency to form secondary decomposition products. Unfortunately, both V and VI were non-distillable blue oils which were difficult to prepare and were therefore not investigated further. It is desirable that a compound to be used for asymmetric photolysis should be a solid, since solids are easily handled and purified. In addition it should be fairly readily prepared since considerable quantities are required. Hence V and VI were definitely unsuitable for further work.

Owing to the scarcity of simple chloronitroso hydrocarbons which are known to exist in the solid state and which possess one asymmetric carbon atom in the molecule (only two such compounds are known), it was decided to carry out the asymmetric photolysis of β-chloro-β-nitrosohexane VII.



VII

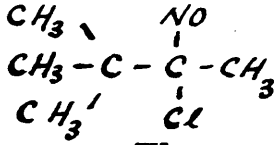
Although this substance is a liquid, it is readily purified by distillation under reduced pressure and is very easily prepared. The photochemistry of this compound was investigated by Dr. J. Cameron[52] in this department and he found the quantum efficiency to be 1.2, so that the time of decomposition would be considerably less than that of IV. He also examined the decomposition products in methyl alcohol and showed that the asymmetry of the molecule was destroyed by the light. Moreover the substance is not very volatile at atmospheric pressure, and being straight-chained there is little risk of rearrangement or secondary reactions occurring in the photochemical decomposition. In addition, since the compound is isomeric with IV, it is of interest to compare the results obtained in an asymmetric photolysis with those obtained previously for IV.

The Asymmetric Photolysis of β-chloro-β-nitrosohexane.

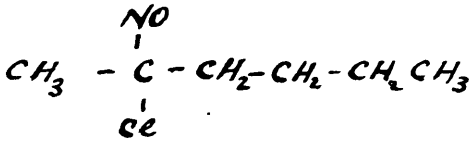
The arrangement for the photolysis was the same as for IV, two cells of 50 cc. capacity and 2 cm. thickness again

being used. They were filled with a 16% solution of VII in methyl alcohol, one being exposed to right-handed and the other to left-handed circularly polarised light until the concentration was 3% (approximately 80% decomposition requiring 30 hours). Owing to the intense absorption, solutions stronger than 3% could not be read accurately in the polarimeter. On examining the solutions to see if any rotation had been developed, a difference of 0.06° was observed. Two more experiments were carried out using 16% solutions, the decomposition again being taken to 80%. The unchanged blue substance was recovered in each case as described for IV and purified by distillation under reduced pressure. Sufficient of the pure blue liquid was recovered from these experiments to make up 16% solutions for the second stage. Again the decomposition was carried to the extent of 80% (i.e., a total extent of 96%), this time in 1 cm. cells. After transferring the solutions to the polarimeter a difference of 0.11° was noted, which was almost double the value observed at the first stage and gives $[\alpha]^{18°}_{5780} = \pm 1.67°$ (c = 3% in methyl alcohol, l = 1). The values for IV after 94% decomposition were $[\alpha]^{18°}_{5780} = \pm 3.5°$.

By comparing the structural formulae of IV and VII, and



IV



VII

the values of $[\alpha]$ obtained, it would appear that the

fractionation is more efficient when there is a bulky group such as the tert. butyl group, in the molecule, than when the molecule is straight chained. The work by Mitchell and Dawson[50] with β -chloro-β-nitroso-$\gamma\gamma$-diphenylbutane, which contains two benzene rings in the molecule, seems to support this view. To verify this, a resolution of the two compounds would be necessary in order to compare their anisotropy factors. This aspect of the problem is considered in Part II of this thesis.

Experimental: Preparation of the Chloronitroso Compounds.

Compounds of the type $R_1-\underset{Cl}{\overset{NO}{\overset{|}{\underset{|}{C}}}}-R_2$ where R_1 and R_2 are simple alkyl radicals, were first prepared by Rheinboldt and Dewald[47] by the action of nitrosyl chloride on the corresponding oxime. They can also be prepared by the action of chlorine on the oxime and this method was used by Mitchell and Cameron[49]. They passed chlorine into a solution of the oxime in hydrochloric acid. Considerably better yields were obtained later by passing chlorine into a solution of the oxime in dry ether, this being the method adopted in the preparations of all chloronitroso compounds about to be described. Since these substances were obtained from the corresponding ketoximes, it was first necessary to prepare the desired ketones.

(a) Preparation of β-chloro-β-nitroso-γγ-dimethylbutane.

The following stages were required:-

(1). Pinacolone was prepared from acetone[53].

(2). By treating the ketone with an aqueous solution of hydroxylamine (prepared by mixing equimolecular amounts of hydroxylamine hydrochloride and sodium hydroxide in water) the oxime was obtained[54]. M.P. 74°C. (Yield, 62%).

(3). The oxime was dissolved in dry ether and chlorine passed in, whereupon the solution became blue and a precipitate of the oxime hydrochloride appeared. Continued passing of the chlorine caused the precipitate to redissolve, and when the

solution was a deep green colour, it was washed repeatedly with water to completely remove the chlorine, dried over sodium sulphate, and the ether evaporated leaving a deep blue solid, m.p. 118°C. (Yield, 40%). As the substance was extremely soluble in all organic solvents, it was very difficult to recrystallise. A few crystals were obtained from methyl alcohol, m.p. 121°C, but only a small fraction of the dissolved substance crystallised out. For ordinary photochemical purposes, however the uncrystallised substance was found to be quite satisfactory.

(b) Preparation of β-chloro-β-nitroso-δδ-dimethylpentane.

In this case methyl neopentyl ketone was required. This ketone was prepared in the following way:-

Tert. butyl alcohol was first dehydrated with 30% sulphuric acid to give isobutylene which immediately dimerised in the acid medium giving mainly a mixture of diisobutylenes (and a few higher polymers)[55]. The separated and carefully dried mixture was fractionally distilled, a 70% yield of the two diisobutylenes, b.p. 100-105°C/729 mm., being obtained.

In the next stage the diisobutylene mixture was oxidised at room temperature with potassium dichromate and sulphuric acid as described by Whitmore[56]. From 60 gms. of the dimer mixture 6 gms. of methyl neopentyl ketone were obtained, b.p. 122-126°C. A semicarbazone was prepared, m.p. 174°C, instead of Whitmore's value of 124°C. (Found: C, 56.2; H, 10.0; N, 24.6. Calc. for $C_8H_{17}ON_3$: C, 56.1; H, 9.9;

N, 24.6%). These results indicate that the compound is the semicarbazone of the required ketone, different in m.p. from Whitmore's and possibly a geometrical isomer of it.

The ketone was treated with an aqueous-alcoholic solution of hydroxylamine (prepared by mixing equivalent quantities of hydroxylamine hydrochloride in water and potassium acetate in alcohol, and filtering off the precipitated potassium chloride), to give the oxime. As the latter was a non-distillable oil, further purification of it was not possible. After drying, therefore, it was dissolved in dry ether and chlorine was passed in giving a deep blue solution. Removal of the ether gave a viscous blue oil which did not solidify. A Stepanow's chlorine estimation was carried out giving a value of 21.4%; theoretical value, 21.7%.

(c). Preparation of γ-chloro-γ-nitroso-$\beta\beta$-dimethylpentane.

Ethyl tert. butyl ketone which was required in this case, was prepared in the following stages:-

(1). Pinacolone was prepared from acetone[53].

(2). The pinacolone was oxidised with sodium hypobromite to give trimethylacetic acid in 70% yield[57]. M.P. 34°C.

(3). By treating 25 gms. of the latter with 70 ccs. of thionyl chloride, 15 gms. of the acid chloride were obtained. B.P. 100-105°C.

(4). The acid chloride was added drop by drop to a concentrated

ammonia
/solution to convert it to the amide. White clouds of ammonium chloride were formed, and a white solid precipitated, which was filtered off and crystallised from alcohol, 7 gms. being obtained. M.P. 153°C. (Literature, M.P. 153°C.)
(5). To prepare the ketone, the trimethylacetamide was added to 2 moles. of ethyl magnesium bromide as described by Whitmore[58]. B.P. 124-126°C. (Yield, 44%).

The oxime was prepared in the usual manner and being a solid, was easily purified from alcohol. M.P. 83°C. (Literature, M.P. 84°C). As before, the oxime was dissolved in dry ether and chlorine passed into the solution. After removing the ether, a deep blue oil was obtained which did not solidify even when placed in a freezing mixture.

(d) Preparation of β-chloro-β-nitrosohexane.

(1). n-Propyl iodide was prepared in the usual way from n-propyl alcohol, red phosphorus and iodine, in 60% yield. B.P. 102°C.
(2). By condensing the iodide with the sodium derivative of ethyl acetoacetate in alcoholic solution, n-propyl ethyl acetoacetate was obtained in 60% yield. B.P. 97-103°C/20 mm.
(3). The latter was boiled for eight hours with a 10% solution of potassium hydroxide, the ketone being distilled in steam. After separating the upper layer of the distillate, it was dried over sodium sulphate and fractionated, the fraction boiling at 114-117°C/755 mm. being collected. (Yield, 55%).

(4). The oxime, which was an oil, was prepared in the usual manner and was purified by distillation under reduced pressure. B.P. 86-89°C/17 mm. (Yield, 64%).

(5). Chlorine was passed into a dry ethereal solution of the oxime until the solution was greenish in colour. The blue liquid remaining after removal of the ether was distilled under reduced pressure from a hot water bath. B.P. 44°C/14 mm. (Yield, 70%).

Part II.

The Problem of Resolving Chloronitroso Acids.

Chloronitroso acids of the type,

$$R - \overset{\overset{NO}{|}}{\underset{\underset{Cl}{|}}{C}} - COOH$$

in which the carboxyl group is linked to the asymmetric carbon atom, do not appear to exist. Attempts to prepare α-chloro-α-nitrosopropionic acid (a), and α-chloro-α-nitroso-ββ-dimethylbutyric acid (b),

$$CH_3 - \overset{\overset{NO}{|}}{\underset{\underset{Cl}{|}}{C}} - COOH \qquad (a)$$

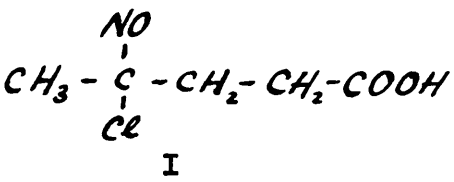
$$(CH_3)_3C - \overset{\overset{NO}{|}}{\underset{\underset{Cl}{|}}{C}} - COOH \qquad (b)$$

from the oximes of pyruvic and trimethylpyruvic acids respectively, were unsuccessful owing to the instability of (a) and (b). Acids of the type,

$$R - \overset{\overset{NO}{|}}{\underset{\underset{Cl}{|}}{C}} - CH_2 - COOH$$

have not been prepared either. This is probably due firstly to the instability of β-keto acids, and secondly to their tendency to form isoxazolone compounds with hydroxylamine instead of oximes. The isoxazolone compounds, when treated with chlorine, do not give chloronitroso acids. Menthyl esters of β-ketonic acids, however, are readily prepared by heating the ethyl esters with excess menthol[59], and from them the oximes and chloronitroso esters are usually easily obtained. Provided the latter are solid substances, they should be theoretically capable of being resolved.

The first simple chloronitroso acid to be obtained was γ-chloro-γ-nitroso-valeric acid, I,



I

prepared by Mitchell, Schwarzwald and Simpson[51] from the oxime of laevulinic acid. An acid, in which the asymmetric centre is separated from the carboxyl group by two carbon atoms has been previously resolved by Fischer[60], viz., γ-aminovaleric acid. Attempts to resolve I were made in this department by Dr. Simpson[61]. Although he obtained salts with various optically active bases which were crystallisable from organic solvents, no resolution of the acid was achieved. Unfortunately salts formed by chloronitroso acids are very unstable to light and decompose rapidly especially in solution. Decomposition is hastened by heating the solutions, so great care must be taken when recrystallising the salts not to apply too much heat. This means that larger volumes of solvent are required, and a lower percentage of the salt crystallises out at each stage.

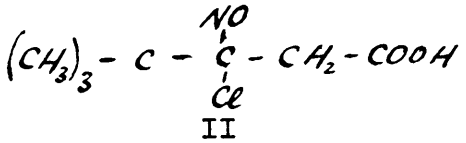
Menthyl esters of chloronitroso acids, however, are much more stable, and if solid, are usually very easily crystallised. The only disadvantage is that having prepared the menthyl ester, it has been found impossible to hydrolyse it in order to recover the free chloronitroso acid. Alkaline hydrolysis immediately decomposes the ester, while acid hydrolysis in the cold (heating causes decomposition), appears quite ineffective.

The first chloronitroso compound to be resolved was 1-menthyl β-chloro-β-nitrosobutyrate by Mitchell and Simpson.[22] They obtained the values $[\alpha]^{18°}_{5660} = -415.4°$ and $[\alpha]^{18°}_{6600} = +484.6°$. From this work it would appear that the menthyl esters of chloronitroso acids would be very suitable for resolution purposes, provided, of course, they were solid substances. The first line of approach, therefore, to the problem of resolving chloronitroso acids, was the preparation of some menthyl and bornyl esters.

A). Experiments with Menthyl and Bornyl Esters of Chloronitroso Acids.

Attempt to prepare 1-menthyl β-chloro-β-nitroso-$\gamma\gamma$-dimethylvalerate.

In Part I of this thesis successful asymmetric photochemical experiments with β-chloro-β-nitroso-$\gamma\gamma$-dimethylbutane were described. In order to predict what size of rotations should be obtained, it was decided to attempt a resolution of the acid which most closely corresponded to that compound, viz:-



II

The β-keto ethyl ester was first synthesised in a series of stages from pinacolone. Hydrolysis of the ester with cold potassium hydroxide gave the very unstable β-keto acid, and

attempts to obtain the oxime of the latter only resulted in the formation of the isoxazolone compound. Thus it was decided to prepare the menthyl ester of II, which, if a solid, should be capable of being resolved. The keto menthyl ester was readily made from the ethyl ester, but attempts to form the oxime were unsuccessful. Menthol appeared to be hydrolysed off and the isoxazolone compound obtained above was again produced.

In an attempt to make a scale model of the molecule of β-keto-$\gamma\gamma$-dimethylvaleric acid, it was found that owing to the combined steric hindrance of the tertiary butyl and $-CH_2COOH$ groups, the oxime group could not be inserted in the molecule without a great deal of strain. The model of the oxime of β-keto butyric acid could be made fairly readily. Thus the difficulty in preparing the oxime of the menthyl ester of β-keto-$\gamma\gamma$-dimethylvaleric acid is probably accounted for by steric hindrance.

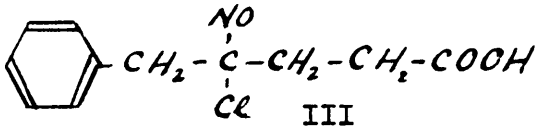
Attention was then directed to the menthyl and bornyl esters of γ-ketonic acids.

Menthyl and Bornyl esters of γ-chloro-γ-nitrosovaleric acid.

These two esters had been previously prepared in this department by Dr. Simpson[61] who found that they were viscous blue oils which did not solidify. With the introduction since then of an improved method for preparing chloronitroso compounds by chlorinating the oxime in sodium-dried ether, it was decided

to repeat this work, in the hope that by employing this method, the chloronitroso esters might be obtained as crystalline solids. In spite of every precaution being taken to ensure the substances being pure and dry, the chloronitroso compounds were again found to be blue oils which did not solidify even after several months in the refrigerator. It was therefore concluded that these substances must exist as liquids, and were therefore unsuitable for resolution purposes.

Menthyl and Bornyl esters of γ-chloro-γ-nitroso-δ-phenyl-valerid acid, III.

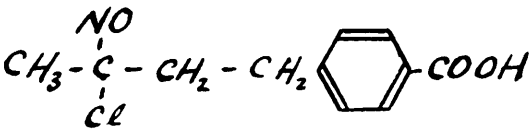


III

By increasing the molecular weight of the chloronitroso acid with the introduction of a phenyl group, it was hoped that a solid menthyl or bornyl ester would be obtained. Accordingly, δ-phenyl laevulinic acid was synthesised and from it the menthyl ester. Although the latter was a crystalline solid and gave a solid oxime, a viscous blue oil was obtained on chlorinating the oxime in dry ether. The bornyl ester was also an oil.

In order to ensure that a solid chloronitroso menthyl ester would be obtained, the next acid investigated was one isomeric with III, with the carboxyl group attached to the benzene ring.

Menthyl ester of γ-chloro-γ-nitroso-α-(p-carboxyphenyl)-butane, IV.



IV

The keto-acid was synthesised in a series of stages from p-toluidine, and from it the menthyl ester was prepared. The latter was an oil as was also the oxime formed from it, but the chloronitroso compound was a blue crystalline solid which crystallised in splendid blue needles from methyl or ethyl alcohol. M.P. 44-48°C. $[\alpha]_{5200}^{18^\circ}$ = -79°C. (ℓ = 1, c=2% in ethyl alcohol). An attempt was made to resolve the ester by crystallising it six times from methyl alcohol, the melting point and the specific rotation being noted after each crystallisation. It was found that neither of them changed indicating that the compound was not being resolved. Crystallisation from methyl alcohol, acetone, and n-hexane also failed to resolve the ester. (It is possible in this case that the chances of resolution may be adversely influenced by the distance of the menthyl group from the asymmetric centre.)

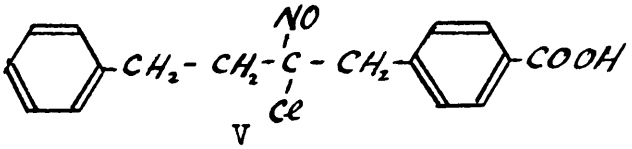
Attempts to resolve chloronitroso acids by means of l-menthol and l-borneol having proved unsuccessful, a second approach to the problem was adopted.

B). Fractional Crystallisation of Salts of some Chloronitroso Acids with Optically Active Bases.

"Everyone who has had occasion to make experiments of this kind, knows the disillusioning obstacles often presented to him and the serious difficulties to be overcome." Jaeger[62].

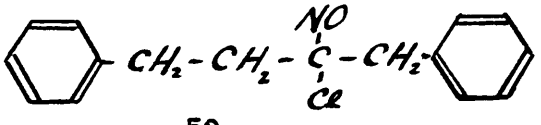
It has already been pointed out that although menthyl esters of chloronitroso acids are much more stable than salts with alkaloid bases, nevertheless, having resolved the ester, it is not possible to liberate the free chloronitroso acid by hydrolysis owing to the molecule decomposing. So far no chloronitroso acid has been obtained optically active. The advantage of using bases to resolve these acids is that the free acid is easily recoverable in a pure state from the salt.

Attempt to resolve β-chloro-β-nitroso-α(p-carboxyphenyl)-δ-phenylbutane, V.



V

This acid was selected for resolution purposes as it was very similar in structure to β-chloro-β-nitroso-α-δ-diphenylbutane,



with which Mitchell and Dawson[50] carried out successful asymmetric photochemical experiments. Unfortunately, the

synthesis of V was rather involved requiring eight stages, the last five being new. Moreover, as the yields at some of the intermediate stages were extremely poor, insufficient of the final product was obtained to allow of an extensive investigation.

Salt formation with alkaloid bases.

With brucine a green solid was obtained indicating that decomposition had occurred. Both ephedrine and quinine gave pale blue salts immediately when mixed with V in ethereal solution. No suitable solvent could be found for crystallising the ephedrine salt, but the quinine salt crystallised well from methyl acetate. M.P. 152°C (with decomposition).

Attempted resolution of V by crystallisation of the quinine salt from methyl acetate.

To 1.5 gms. quinine dissolved in dry ether, 1.5 gms. of V in dry ether were added giving 2.7 gms. of a pale blue salt. The salt was very unstable and if left in solution for more than a few hours, decomposed. A 2% solution in alcohol gave $[\alpha]_{570\mu\mu}^{18^\circ} = -114.4^\circ$. After one crystallisation from methyl acetate $[\alpha]_{570\mu\mu}^{18^\circ} = -114^\circ$ and after two crystallisations $[\alpha]_{570\mu\mu}^{18^\circ} = -112^\circ$ no appreciable change being observed. The free acid was recovered from the quinine salt by treating it with dilute hydrochloric acid and extracting the liberated acid with ether. After removing the ether, the blue acid was crystallised from methyl alcohol, but on examining a solution in alcohol in the polarimeter, no trace of rotation could be observed. Lack of

material prevented further work being carried out with this substance.

The Partial Resolution of γ-chloro-γ-nitrosovaleric acid.

Since considerable quantities of material are usually required for resolution purposes, the above acid was selected, being readily obtained from the oxime of laevulinic acid. It has already been mentioned that previous attempts to resolve this acid were unsuccessful. An extension of this work has led to a partial resolution.

Salt formation of γ-chloro-γ-nitrosovaleric acid.

Attempts were made to form salts with the following alkaloid bases:- brucine, cinchonine, cinchonidine, quinine and quinidine. With brucine a pale blue salt was obtained which rapidly turned green, and on dissolving it in various solvents, white crystals (probably brucine hydrochloride) were deposited, indicating decomposition. Cinchonine, cinchonidine, and quinidine, gave sticky blue oils, but with quinine a blue crystalline salt was formed, so this base was again chosen for the resolution.

Preparation of the quinine salt.

To a solution of quinine in dry ether containing a little alcohol to complete solution was added an equimolecular quantity of γ-chloro-γ-nitrosovaleric acid in dry ether. In half an hour splendid blue crystals of the salt were obtained and were purified from alcohol. M.P. 120-124°C. (Found: C, 61.2;

H, 6.6; N, 8.4. $C_{25}H_{32}O_5N_3Cl$ requires: C, 61.3; H, 6.5; N, 8.6%*). Polarimetric examination of a 2% solution of the salt in methyl alcohol gave $[\alpha]^{18^\circ}_{5700} = -136^\circ$. Many solvents were tried for the crystallisation of the salt but only from ethyl alcohol and methyl acetate could any crystals be obtained.

Partial Resolution of the quinine salt by crystallisation from ethyl alcohol.

46 gms. of the quinine salt were prepared and crystallised six times from alcohol, the work being done as far as possible in darkness owing to the great sensitivity of the substance to light. Care was also taken not to warm the solutions above 40°C during the crystallisations as the salt was liable to decompose when strongly heated. Thus considerable volumes of alcohol were required for each crystallisation and only 50% of the salt was obtained at each stage. The specific rotations of 2% solutions of the salt in methyl alcohol at different stages are given below.

No. of crystallisation	0	1st	2nd	3rd	4th	5th	6th
$[\alpha]^{18^\circ}_{5700}$	-136°	-134°	-130°	-127°	-124°	-122°	-120°

From these results it can be seen that there was a slow decrease in the specific rotation after each crystallisation. Owing to the decomposition of the salt near its melting point, it was not possible to follow the progress of the resolution

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* Analytical results for new substances are given according to the convention adopted in the Journal of the Chemical Society.

by that means. Since only 1 gm. of the salt remained after the 6th crystallisation, the chloronitroso acid was liberated by decomposing the salt with dilute hydrochloric acid and was extracted with ether. After removing the ether and crystallising the acid from n-hexane, a solution in alcohol was examined in the polarimeter, the results being given in Table II(a). The small positive rotation indicates that a partial resolution has been achieved.

Since the decrease in the specific rotation of the salt appeared to be very slow using alcohol as the solvent for crystallising, it was decided to try methyl acetate.

Partial resolution of quinine salt by crystallisation from methyl acetate.

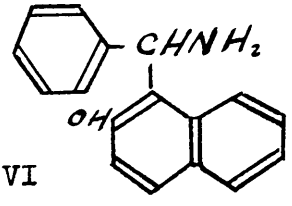
140 gms. of the quinine salt were prepared and dissolved in methyl acetate (550 ccs.). The solution was allowed to stand for 2-3 hours in the refrigerator, when a crop of crystals, A (56 gms.), was obtained. By concentrating the solution under reduced pressure a further 47 gms. A_1, came down.

A was dissolved again and the solution cooled giving B (33 gms.). A_1 was dissolved giving B_1. B was then crystallised 5 times from methyl acetate giving C, D, E, F, G. G amounted to 3 gms. and a 2% solution in methyl alcohol gave $[\alpha]_{570}^{18^\circ} = -118.6^\circ$. B_1 was crystallised seven tines giving C_1, D_1, E_1, F_1, G_1, H_1, I_1, I_1 amounting to 1.8 gms., and a 2% solution in methyl alcohol gave $[\alpha]_{570}^{18^\circ} = -119^\circ$. I_1 was

therefore combined with G which was crystallised again from methyl acetate giving H (1.8 gms.). $[\alpha]^{18^\circ}_{5700}$ for H = -116.5°, indicating a decrease in the specific rotation of 20° after eight crystallisations. As the specific rotation had not reached a constant value, the resolution did not appear to be complete, but owing to the very slow decrease and the small quantity of the salt left, it was decided to recover the chloronitroso acid at this stage. This was effected as described previously and after crystallising the acid from n-hexane, a solution in alcohol was examined in the polarimeter. Rotation and ellipticity readings were taken and these are tabulated in Table II(b) and (c), the rotatory dispersion and ellipticity curves being shown in Fig.2. The rotatory dispersion curve shows the presence of a Cotton effect due to the nitroso group. Owing to the intense absorption of the light by the solution, observations beyond 6500 A could not be made.

A partial resolution of γ-chloro-γ-nitrosovaleric acid has thus been achieved.

Salt formation of γ-chloro-γ-nitrosovaleric acid with β-naphthol phenylaminomethane.



VI

Since the base VI is fairly readily prepared and resolved, it was decided to investigate the possibility of its use as a resolving agent for chloronitroso acids.

Table II

Rotatory Dispersion of γ-chloro-γ-nitrosovaleric acid.

a). After 6 crystallisations of quinine salt from ethyl alcohol.

(c = 2.50 gms./100 ccs. alcohol. t = 18°C. l = 10 cm.).

λ	α	$[\alpha]$
5200	+0.12°	+4.2°
5300	+0.14	+5.6
	c = 1 gm./100 ccs. l = 10 cm.	
5400	+0.08	+8
5500	+0.10	+10
5600	+0.13	+13
5700	+0.16	+16
5800	+0.13	+13

b). After 8 crystallisations of quinine salt from methyl acetate.

(c = 1.06 gms./100 ccs. t = 18°C l = 10 cm.

λ	α	$[\alpha]$
5200	+0.05	+4.7
5300	+0.08	+7.5
5400	+0.10	+9.4
5500	+0.12	+11.3
5600	+0.16	+15.1
5700	+0.21	+19.8
	l = 2.5 cm.	
5800	+0.05	+19.0
5900	+0.04	+15.1
6000	+0.05	+19.0
6100	+0.06	+22.7
6200	+0.08	+30.2
6300	+0.05	+19.0
6400	+0.01	+3.8
6500	-0.07	-26.3

FIG. 2.

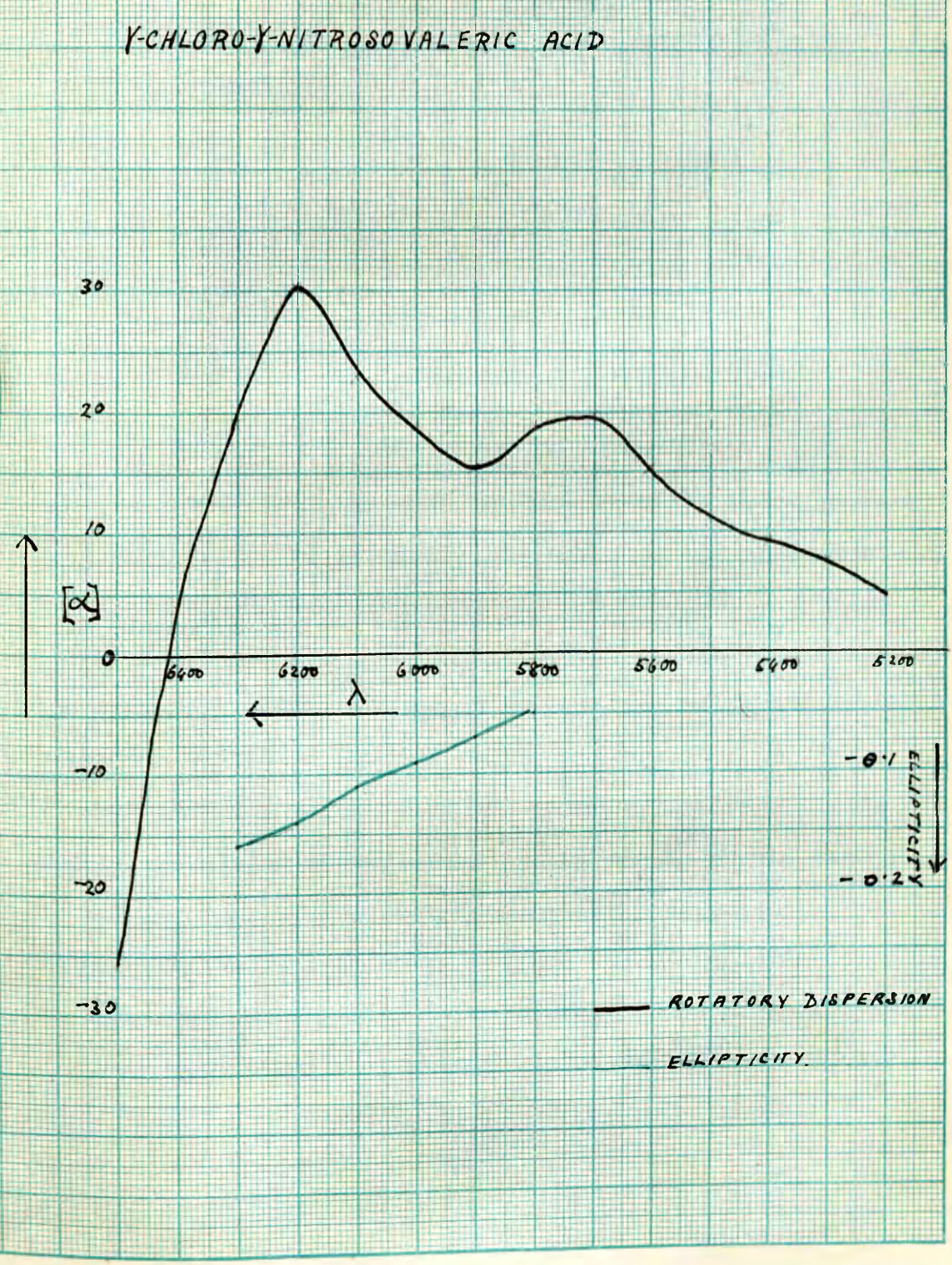

γ-CHLORO-γ-NITROSOVALERIC ACID
30
20
10
[α]
0
-10
-20
-30
6400
6200
6000
5800
5600
5400
5200
λ
-0·1
-0·2
ELLIPTICITY
ROTATORY DISPERSION
ELLIPTICITY.

Table II (Contd.)

c). Ellipticity of γ-chloro-γ-nitrosovaleric acid.

(c = 1.06 gms./100 ccs. ethyl alcohol. l = 2.5 cm.)

λ	Ellipticity
5700	0
5800	-0.05°
5900	-0.07
6000	-0.09
6100	-0.11
6200	-0.14
6300	-0.16

It is desirable that a base to be used for such a purpose should have a) a fairly high specific rotation, and b) a high molecular weight, since owing to the intense absorption of chloronitroso acids in the visible, only very dilute solutions can be accurately read in the polarimeter. The base VI fulfils both conditions fairly well, having a molecular weight of 249 and a specific rotation of +58°.

By adding a solution of γ-chloro-γ-nitrosovaleric acid in dry ether to an equimolecular amount of the base in dry ether, a pale blue salt immediately precipitated. It crystallised well from ethyl acetate but the solution in this solvent decomposed within a few hours. M.P. of salt = 115°C (with decomposition). (Found: C, 63.6; H, 5.7; N, 6.8. $C_{22}H_{23}O_4N_2Cl$ requires: C, 63.7; H, 5.6; N, 6.8%).

Crystallisation of salt from ethyl acetate.

Using 4.7 gms. of the optically active base and 3.12 gms. of the chloronitroso acid, 6.5 gms. of the salt were prepared. $[\alpha]^{18°}_{5200} = +64.12°$. (c = 2% in methyl alcohol, l = 1). After one crystallisation from ethyl acetate, $[\alpha]^{18°}_{5200} = +64°$. After two crystallisations, $[\alpha]^{18°}_{5200} = 61.8°$ and after three, $[\alpha]^{18°}_{5200} = 59.8°$. Thus a slight decrease in the specific rotation was observed, but again the progress of the resolution appeared to be very slow. After acidifying the salt and recovering the free acid, only a very small negative rotation was observed, so no further work with this salt was carried out.

From the above attempts to resolve γ-chloro-γ-nitroso-valeric acid, it can be seen that a complete resolution, using the optically active bases mentioned, would be a long and tedious task. It was thought that more promising results might be obtained by introducing a phenyl group into the molecule. γ-chloro-γ-nitroso-δ-phenylvaleric acid was therefore next investigated.

The Resolution of γ-chloro-γ-nitroso-δ-phenylvaleric acid.

This acid was prepared from the oxime of δ-phenyl laevulinic acid. Its salt formation with various bases was first investigated. Brucine, quinine, and other alkaloids only gave sticky blue oils. A crystalline salt was obtained with ephedrine, but no suitable solvent could be found for its crystallisation. With β-naphthol phenylaminomethane, a pale

blue salt was immediately formed in ethereal solution, which crystallised in blue silky needles from ethyl acetate. M.P. 105°C (with decomposition). (Found: C, 68.8; H, 5.4; N, 5.7. $C_{28}H_{27}O_4N_2Cl$ requires: C, 68.5; H, 5.5; N, 5.7%).

Since the synthesis of this acid was rather involved, a preliminary attempt to resolve it with the base VI was first carried out.

Preliminary Attempt.

12 gms. of the chloronitroso acid were prepared and combined with 12.5 gms. of the optically active base in dry ether solution to give 17 gms. of the salt. M.P. 102-105°C. The latter was then crystallised four times from ethyl acetate, care being taken to avoid warming the solution above 40°C. Below are recorded the specific rotations of 2% solutions of the salt in methyl alcohol at the various stages.

No.of crystn.	0 (orig. subs.)	1	2	3	4
$[\alpha]_{5200}$	+50°	59.8°	69.9°	83°	86°
$[\alpha]_{5600}$	+38°	52.3°	66°	83°	90°

After the fourth crystallisation the melting point of the salt was 110-112°C. Owing to insufficient material, further crystallisations were not possible, but the considerable increase in both the melting point and the specific rotation indicated that the salt was being resolved. It was therefore acidified with dilute hydrochloric acid to liberate the chloronitroso acid, which was then extracted with ether and

purified by crystallisation from n-hexane. M.P. 76°C. A solution of the acid was examined in the polarimeter, rotation and ellipticity readings being taken, and these are shown in Table III (a) and (b). The rotatory dispersion and ellipticity curves are shown in Fig.3.

Completion of Resolution.

In order that the resolution might be taken to completion, 66 gms. of the chloronitroso acid were synthesised and 69 gms. of the optically active base. To a solution of the latter in dry ether, a solution of the acid in ether was added, and the pale blue salt which separated was filtered off. Concentration of the ether filtrate gave more of the salt, a total yield of 115 gms. being obtained. M.P. 102-105°C.

Fractional crystallisation of the salt from ethyl acetate.

The salt was dissolved in 1050 ccs. of ethyl acetate with gentle warming and on cooling 56 gms. of crystals, A, were obtained. Concentration of the mother liquor gave a further 21 gms. (A_1). An attempt to concentrate the solution still further resulted in its decomposition.

A was dissolved and on cooling gave 28 gms. of B, m.p. 107-110°C. After concentrating the mother liquor, a further crop of 15 gms. was obtained. A_1 was recrystallised giving 15 gms. (B_1), which was then combined with the second crop from A.

B was crystallised four times giving C (18 gms.), D (10 gms.), E (7 gms.), F (4 gms.), the second crops from each of

Table III.

a). Rotatory Dispersion of γ-chloro-γ-nitroso-δ-phenyl-valeric acid. (After four crystallisations of the salt from ethyl acetate.)

(c = 2.022 gms./100 ccs. alcohol. t = 18°C. l = 10 cm.

λ	α	$[\alpha]$
5000	+2.59°	+128°
5200	+3.00	+148
5300	+3.26	+159
5400	+3.50	+171.
c = 0.881 gms./100 ccs.		
5500	+1.50	+186
5600	+1.60	+198
5700	+1.71	+211
c = .2022 gms./100 ccs.		
5800	+0.47	+232
5900	+0.49	+242
6000	+0.45	+222
6100	+0.43	+213
6200	+0.40	+198
6300	+0.37	+183
6400	+0.31	+153
6500	-0.05	- 25
6600	-0.45	-223
6700	-0.55	-272
6800	-0.46	-228
6900	-0.33	-163

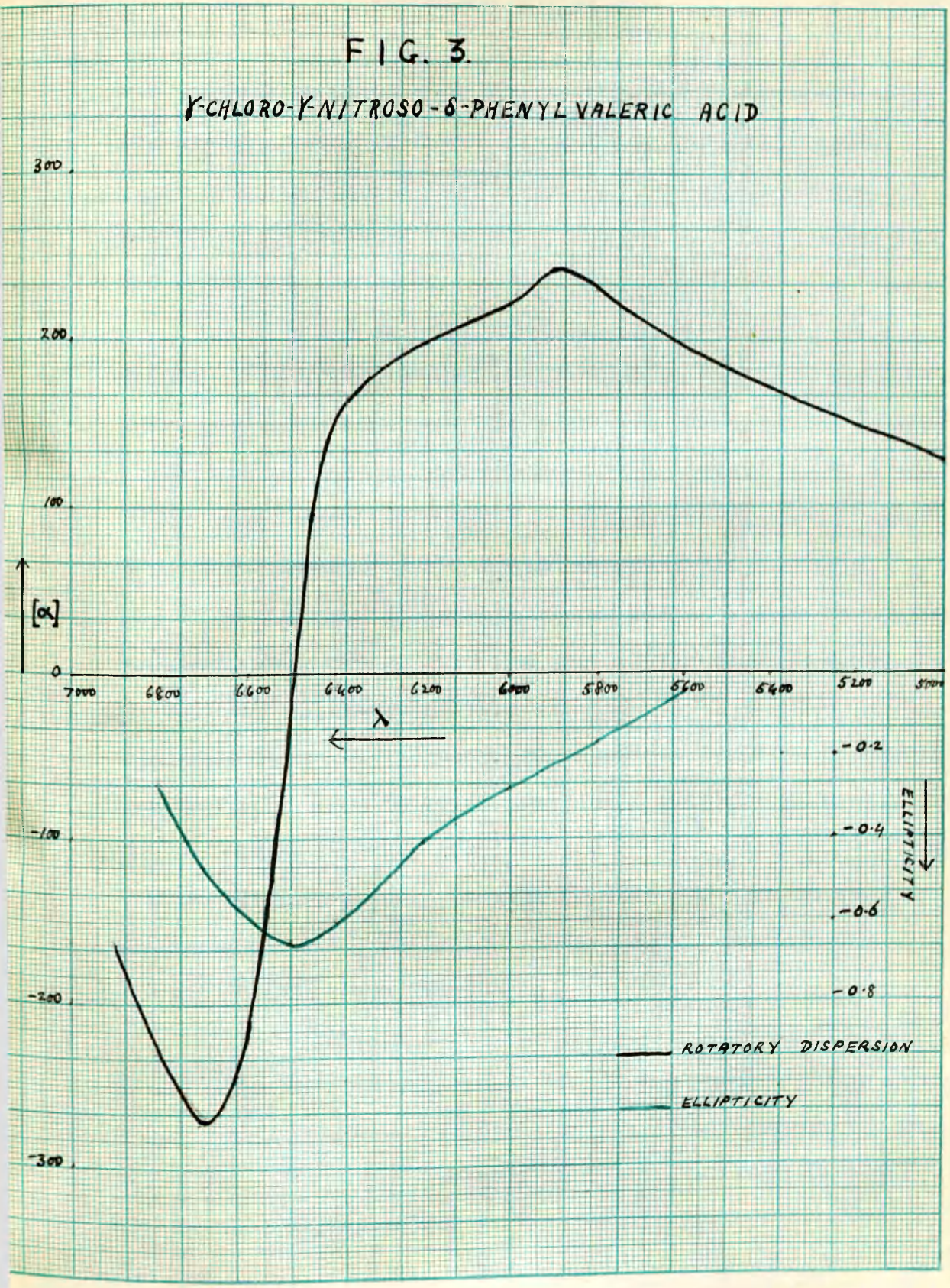
b). Ellipticity.

c = 0.1618 gms./100 ccs. ethyl alcohol. l = 10 cm.

λ	Ellipticity
52	0
54	0
56	-0.05°
58	-0.16
60	-0.27
62	-0.41
64	-0.60
65	-0.65
67	-0.47
68	-0.26

FIG. 3.

γ-CHLORO-γ-NITROSO-δ-PHENYL VALERIC ACID



these being combined with C_1, D_1, E_1, and F_1, respectively. The melting point of F was 110-112°C and $[\alpha]^{18°}_{5600} = 95°$. F_1 was crystallised a further three times giving 2 gms. of substance of the same specific rotation as F with which it was therefore combined.

F (6 gms.) was recrystallised giving G (4.5 gms.). The melting point did not rise any further as the salt decomposed above 112°C, but the specific rotations continued to increase. G was crystallised a further three times giving H (2. 5 gms.), I (1.5 gms.) and J (0.8 gms.). The values of $[\alpha]^{18°}_{5600}$ for H, I, and J, were 108.5°, 109.6° and 111° respectively.

As the specific rotations did not appear to be increasing much more, and as only 0.8 gms. of the salt remained, no further crystallisations were attempted. After ten crystallisations from ethyl acetate the specific rotation at 5200 A had increased from 50.3° to 104°, and at 5600 A from 38.4° to 111°. Table IV shows the increase of $[\alpha]_{5200}$ and $[\alpha]_{5600}$ with each crystallisation. It will be observed that at the top of the table $[\alpha]_{5200}$ is greater than $[\alpha]_{5600}$, whereas the opposite is the case lower down.

The salt, after ten crystallisations, was acidified with dilute hydrochloric acid and the acid recovered as described previously. After crystallisation from n-hexane the melting point was 79°C. A solution of the resolved acid in ethyl alcohol was then examined in the polarimeter.

Table IV

Rotations of the salt (of γ-chloro-γ-nitroso-δ-phenylvaleric acid with β-naphthol phenylaminomethane) after successive crystallisations from ethyl acetate).

(c = 2.008 gms./100 ccs. methyl alcohol. t = 18°C. l = 10 cm.)

Number of crystallisation	α 5200	α 5600	$[\alpha]$ 5200	$[\alpha]$ 5600
0	+1.01°	+0.77°	+50.3°	+38.4°
1	1.14	0.97	56.8	48.3
2	1.34	1.26	66.7	62.8
3	1.43	1.36	71.2	67.7
4	1.59	1.54	79.2	76.7
5	1.68	1.73	83.7	86.2
6	1.81	1.91	90.2	95.1
7	1.97	2.09	98.13	104.1
8	2.05	2.18	102.1	108.6
9	2.08	2.21	103.6	110.1
10	2.09	2.22	104.1	110.6

Rotatory Dispersion.

In this case, as in previous cases where rotations have been recorded in this thesis, the observations were made visually with a spectropolarimeter constructed from a Hilger polarimeter and Zeiss-Winkel monochromator. A 100 c.p. Pointolite lamp served as light source. The readings are given in Table V and the rotatory dispersion curve is shown in Fig.4. Again the curve is anomalous showing the presence of a Cotton effect due to the nitroso group. Owing to the intense absorption by the solution at wave lengths 6400 - 7000A, it was difficult to take accurate readings in this region.

Circular Dichroism.

Ellipticity readings were taken as before with the spectropolarimeter used for the rotation measurements but with a $\lambda/4$ plate inserted behind the Lippich polarising system. The $\lambda/4$ plate was controlled by a similar arrangement to the analyser fine adjustment, both regulating screws being fitted with graduated drums.

The ellipticity measurements were carried out in the manner described in Mitchell's "Cotton Effect and Related Phenomena", London 1933, p.44.

(1). An angle of 5° (greater than the ellipticity to be measured), was chosen for the half shadow angle.

(2). The analyser was adjusted to its zero position.

(3). The $\lambda/4$ plate was introduced and oriented by the fine adjustment to maintain equal illumination.

Table V.

Rotatory Dispersion of γ-chloro-γ-nitroso-δ-phenylvaleric acid

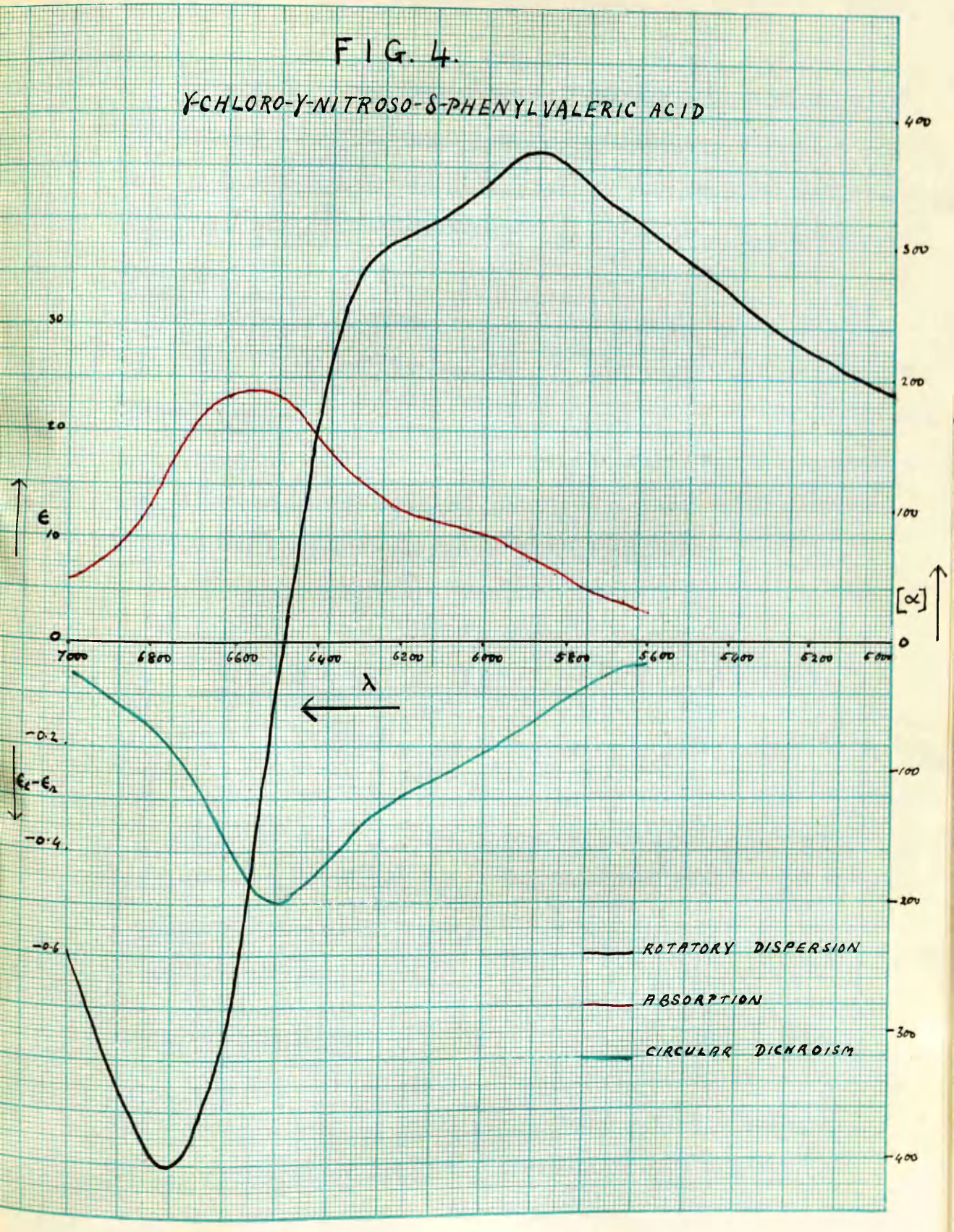
(c = 2.004 gms./100 ccs. alcohol. t = 18°C)

l = 10 cm.

λ	α	[α]
5000	+3.85°	+192.2°
5100	+4.11	+205.1
5200	+4.42	+220.6
5300	+4.80	+239.5
c = 0.681 gms./100 ccs.		l = 6 cm.
5400	+1.09	+266.8
5500	+1.18	+288.8
5600	+1.27	+310.9
5700	+1.36	+332.9
5800	+1.48	+362.0
5900	+1.52	+371.9
6000	+1.43	+349.9
6100	+1.32	+323.0
	l = 2 cm.	
6200	+0.52	+306.0
6300	+0.48	+282.0
6400	+0.30	+176.3
6500	-0.07	- 41.1
6600	-0.47	-276.2
6700	-0.65	-381.9
6800	-0.67	-393.8
6900	-0.55	-323.2
7000	-0.40	-235.1

FIG. 4.

Y-CHLORO-Y-NITROSO-δ-PHENYLVALERIC ACID



(4). The $\lambda/4$ plate was removed, the solution introduced, and the rotation reading taken in the usual way.

(5). The $\lambda/4$ plate was reintroduced, and when the solution exhibited circular dichroism the equality of illumination was destroyed.

(6). Equality of illumination was restored by turning both the $\lambda/4$ plate and the analyser in the same direction through the same angle. This angle gave the measure of the ellipticity.

The measured ellipticity angle was converted to radians and the circular dichroism, $\epsilon_l - \epsilon_r$, calculated from the equation referred to in the introduction, viz.,

$$\epsilon_l - \epsilon_r = \frac{4 \times \tau \times .4343}{c \times l}$$

where τ = angle in radians, c = conc. in gm.mols./l, and l = length of layer of solution in cms.

A correction for the circular dichroism exhibited by the glass ends of the tube was measured and applied. In Table VI the values of the ellipticity and circular dichroism are recorded and Fig.4 shows ($\epsilon_l - \epsilon_r$) graphed against the wavelengths. (See also Fig.5.). The curve is seen to consist of two overlapping bands.

Absorption Spectrum.

The absorption spectrum of a 2% solution of the inactive chloronitroso acid in ethyl alcohol was examined using a Hilger Spekker Photometer in conjunction with a glass

spectrograph. The wave lengths of points of equal intensity on the photographic plates were accurately determined by means of the Hilger microphotometer. Table VII gives the absorption data and the corresponding curve is shown in Fig. 4 and Fig.6.

Since the wave length of ϵ_{max} did not correspond with that of $(\epsilon_{\ell} - \epsilon_{r})_{max}$, and because of the shape of the absorption curve, the latter has been represented in Fig.6 as the sum of three components. Some justification for this procedure is to be found in the absorption band of another nitroso compound. (Cf. Nitrosyl chloride - Goodeve and Katz[63]).

Table VI.

Circular Dichroism of γ-chloro-γ-nitroso-δ-phenylvaleric acid.

(c = 0.681 gms./100 ccs. ethyl alcohol. l = 2.5 cm. t = 18°C).

λ	Ellipticity	$\epsilon_l - \epsilon_r$
5400	-0.05°	-0.022
5500	-0.07	-0.030
5600	-0.11	-0.051
5700	-0.16	-0.069
5800	-0.25	-0.108
5900	-0.35	-0.151
6000	-0.49	-0.211
6100	-0.59	-0.254
6200	-0.69	-0.297
6300	-0.83	-0.357
6400	-1.02	-0.439
6500	-1.13	-0.486
6600	-0.97	-0.417
6700	-0.62	-0.267
6800	-0.38	-0.164
6900	-0.24	-0.103
7000	-0.13	-0.056

Table VII.

Absorption of γ-chloro-γ-nitroso-δ-phenylvaleric acid in ethyl alcohol.

Concn. = .07736 gm.mols./l ℓ = 1 cm.

λ		ϵ
7190	5480	2.59
7100	5660	3.88
7025	5770	5.17
6970	5830	6.41
6930	5890	7.76
6890	5950	9.05
6860	6020	10.34
6830	6140	11.63
6810	6230	12.93
6790	6270	14.22
6770	6310	15.52
6755	6345	16.81
6740	6370	18.09
6725	6400	19.39
6700	6430	20.68
6670	6460	21.98
6620	6500	23.27

Mathematical Representation of Circular Dichroism and Absorption Curves.

Circular Dichroism Analysis.

By employing the equation

$$\epsilon_l - \epsilon_r = (\epsilon_l - \epsilon_r)_{max} e^{-\left(\frac{\lambda-\lambda_0}{\theta}\right)^2} \quad \ldots (1)$$

where θ is a parameter embodying the half width of the band, the curve of circular dichroism was analysed into two normal frequency components. In order to do this, the positions of the maxima of the two components and the wave length at which $\epsilon_l - \epsilon_r$ is half the maximum value of the component curve were arbitrarily assumed, and by trial and error the best fit for the observed curve was obtained after summing the two component curves.

Large Component Curve

Assume λ_0 (i.e., where $\epsilon_l - \epsilon_r$ is a maximum) $= 6500$

$$\begin{cases} (\epsilon_l - \epsilon_r)_{max} = .47 \\ \epsilon_l - \epsilon_r = .235 \end{cases}$$

$\lambda = 6730$ i.e., $\lambda - \lambda_0 = 230.$

From equation (1) we have, $.235 = .47\, e^{-\left(\frac{230}{\theta}\right)^2}$

which gives a value of 276 for θ.

Substituting again in (1) we have,

$$\log x = \log .47 - \frac{D^2}{276} \times .4343$$

where D is the difference in wave length between the maximum and a point on the curve where the circular dichroism has the value x. By giving D the values 100, 200, 300, 400, 500, x was calculated, and the values obtained are shown in Table VIII (a).

and are graphed in Fig.5.

Small Component Curve.

Assume $\lambda_o = 6040$ $(\epsilon_\ell - \epsilon_r)_{max} = .184$

$\lambda = 6280$ $\epsilon_\ell - \epsilon_r = .092$ $\therefore \theta = 288$

Results for this curve are shown in Table VIII(b) and graphed in Fig.5. It can be seen from this figure that the sum of the two component curves agrees well with the experimental curve.

Absorption Curve Analysis.

The absorption curve was assumed to consist of three components of the type given by the equation:-

$$\epsilon = \epsilon_{max}\, e^{-\left(\frac{\lambda-\lambda_o}{\theta}\right)^2}$$

For the large component, $\lambda_o = 6525$, $\epsilon_{max} = 22$, $\theta = 276$

For the small short wave component, $\lambda_o = 6000$, $\epsilon_{max} = 9.4$, $\theta = 288$

For the other small component, $\lambda_o = 6850$, $\epsilon_{max} = 6.4$, $\theta = 300$

The results obtained from this equation are shown in Table IX and the curves in Fig.6. Again there is fairly close agreement between the addition and experimental curves.

Anisotropy Factor.

For the large component curves, $g = \frac{(\epsilon_\ell - \epsilon_r)_{max}}{\epsilon_{max}} = \frac{.47}{22} = .023$

For the small components, $g = \frac{.184}{9.4} = .02.$

This means that there is a difference of about 2% between the absorption of right and left-handed circularly polarised light.

Table VIII

Analysis of Circular Dichroism Curve.

a). Larger Component: $\lambda_o = 6500$; $(\epsilon_l - \epsilon_r)_{max} = 0.47$; $\theta = 276$

λ	$\epsilon_l - \epsilon_r$
6500	0.470
6600	0.412
6400	
6700	0.278
6300	
6800	0.144
6200	
6900	0.058
6100	
7000	0.018
6000	

b). Smaller Component: $\lambda_o = 6040$; $(\epsilon_l - \epsilon_r)_{max} = 0.184$; $\theta = 288$.

λ	$\epsilon_l - \epsilon_r$
6040	0.184
6140	0.163
5940	
6240	0.114
5840	
6340	0.062
5740	
6440	0.027
5640	
6540	0.009
5540	

FIG. 5.

CIRCULAR DICHROISM

γ-CHLORO-γ-NITROSO-δ-PHENYL VALERIC ACID

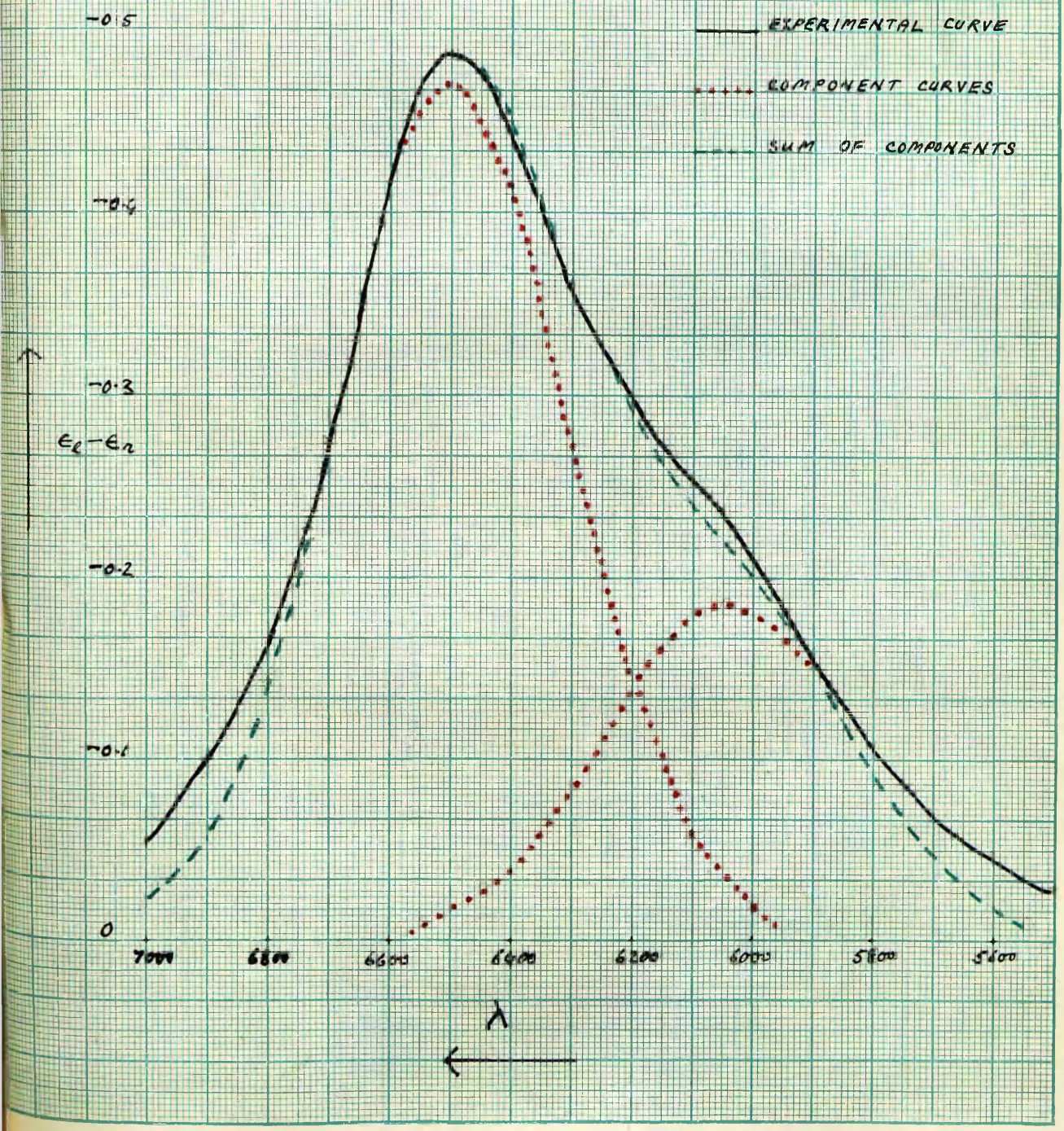


Table IX.

Analysis of Absorption Curve.

a). Large Component: $\lambda_o = 6525$; $\epsilon_{max} = 22$; $\theta = 276$

λ	ϵ
6525	22
6625	19.30
6425	
6725	13.01
6325	
6825	6.75
6225	
6925	2.69
6125	
7025	0.82
6025	

b). Small Component (on short wave side)

$\lambda_o = 6000$; $\epsilon_{max} = 9.4$; $\theta = 288$.

λ	ϵ
6000	9.4
6100	8.33
5900	
6200	5.80
5800	
6300	3.18
5700	
6400	1.37
5600	
6500	0.46
5500	

c). Small Component (on long wave side)

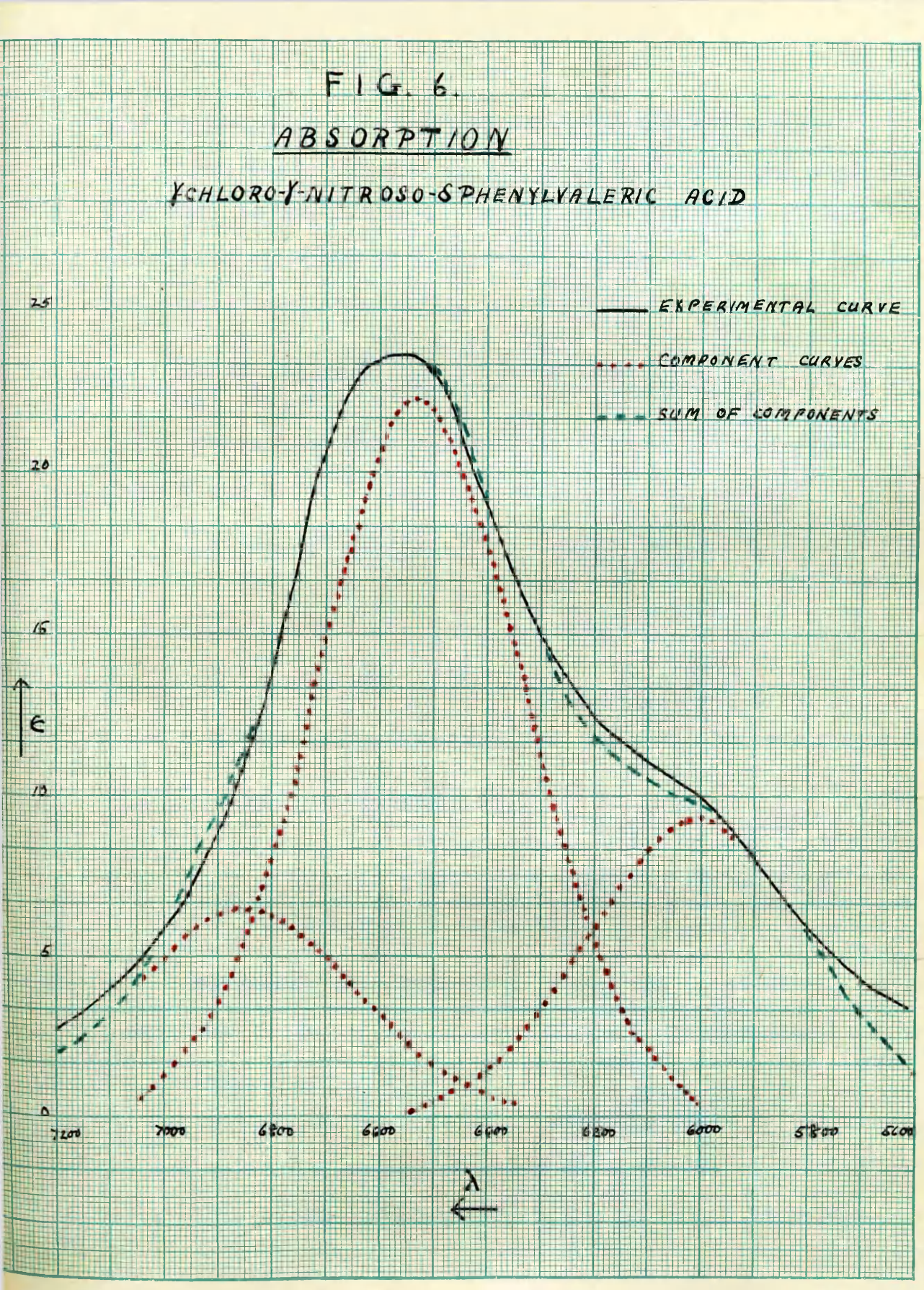
$\lambda_o = 6850$; $\epsilon_{max} = 6.4$; $\theta = 3000$

λ	ϵ
6850	6.4
6950	5.73
6750	
7050	4.10
6650	
7150	2.36
6550	
7250	1.08
6450	
7350	0.40
6350	

FIG. 6.

ABSORPTION

γ-CHLORO-γ-NITROSO-δ-PHENYLVALERIC ACID



Calculation of Partial Rotations due to the NO group.

The contributions to the rotatory dispersion associated with each of the component circular dichroism curves were calculated by means of Lowry and Hudson's modification of Kuhn's equation referred to in the introduction

$$[M] = \frac{100}{2\sqrt{\pi}} \frac{(\epsilon_l - \epsilon_r)_{max}}{\log_{10} e} \frac{\lambda_0}{\lambda} \left[e^{-\left(\frac{\lambda-\lambda_0}{\theta}\right)^2} \int_0^{\frac{\lambda-\lambda_0}{\theta}} e^{x^2} dx + \frac{\theta}{2(\lambda+\lambda_0)} \right] \text{in radians} \quad - \quad (A)$$

Converting this equation to degrees and letting m represent the terms inside the large brackets, we obtain

$$[M] = \frac{100}{2} \cdot \frac{57.296}{.4343} \cdot (\epsilon_l - \epsilon_r)_{max} \frac{\lambda_0}{\lambda} \cdot m$$

$$\therefore [M] = 3723 \cdot (\epsilon_l - \epsilon_r)_{max} \lambda_0/\lambda \cdot m$$

$$\therefore [\alpha] = 3723 \cdot \frac{100}{M} \cdot (\epsilon_l - \epsilon_r)_{max} \frac{\lambda_0}{\lambda} \cdot m \quad - \quad - \quad - \quad (B)$$

where M is the molecular weight of the compound, i.e., M = 241.6.

Large Component of Circular Dichroism.

$(\epsilon_l - \epsilon_r)_{max} = .47$ and occurs at $\lambda = 6500$ $\theta = 276$.

When these values are inserted in equation (B) we have

$$[\alpha] = \frac{3723 \cdot 100}{241.6} \cdot \frac{\cdot 47 \cdot 6500 \cdot m}{\lambda} \quad - \quad - \quad - \quad - \quad (C)$$

To obtain the value of m (i.e., the value of the terms inside the large brackets in equation A) corresponding to λ, the procedure is as follows:-

Six columns are headed as shown in Table X. In column (2) are tabulated values of c for which the corresponding integral is known. These values are contained in column (3).

Now since $c = \frac{\lambda - \lambda_0}{\theta}$ $\therefore$ $\lambda = \lambda_0 + c\theta$

But $\theta = 276$ $\therefore$ $\lambda = \lambda_0 + c.276$

Therefore for an increment of .1 in the value of c, we have an interval in wave length of 27.6. By addition to or subtraction from λ_0, the wave lengths corresponding to different values of c are calculated and are tabulated in column (1).

Column (4) contains the values of $\frac{\theta}{2(\lambda+\lambda_0)}$, and by summing columns (3) and (4), column (5) is obtained. The series of values for m and λ, now obtained, can be substituted in equation (C) to give the desired rotations.

Small Component Curve.

$\lambda_0 = 6040$ $(\epsilon_l - \epsilon_r)_{max} = .184$ $\theta = 288.2.$

We therefore obtain

$$[\alpha] = 3723 . \frac{100}{241.6} . .184 . 6040 . \frac{m}{\lambda}$$

The procedure outlined above is then repeated and a set of partial rotations due to the small band is obtained as shown in Table XI.

By plotting these values, two partial rotation curves are obtained as shown in Fig.7. When these are summed, the addition curve gives the partial rotatory dispersion due to the NO group. By subtracting this curve from the experimental curve, the difference curve obtained represents the rotation of the molecule, the contribution of the NO bands having been subtracted. It can be seen that the difference curve is comparatively smooth, showing that the anomaly due to the nitroso group has been almost eliminated.

Table X.

Partial Rotations calculated from Large Component Curve of Circular Dichroism.

λ	c	$e^{-c^2}\int_0^c e^{x^2}dx$	$\frac{\theta}{z(\lambda+\lambda_0)}$	m	$[\alpha]$
7052	2.0	.3013	.0102	.3115	-207.9
6942	1.6	.4000	.0103	.4103	-278.2
6831	1.2	.5073	.0104	.5177	-356.7
6721	.8	.5321	.0105	.5426	-379.9
6610	.4	.3594	.0105	.3699	-263.4
6500	0	.0000	.0106	.0106	- 7.70
6390	-.4	-.3594	.0107	-.3487	+256.8
6279	- .8	-.5321	.0108	-.5213	+390.6
6169	-1.2	-.5073	.0109	-.4964	+378.7
6058	-1.6	-.4000	.0110	-.3890	+302.1
5948	-2.0	-.3013	.0111	-.2902	+230.0
5837	-2.4	-.2353	.0112	-.2241	+181.0
5727	-2.8	-.1934	.0113	-.1821	+149.9
5534	-3.5	-.1429	.0115	-.1314	+111.9
5936	-4.0	-.1250	.0116	-.1134	+89.91
5258	-4.5	-.1110	.0118	-.0992	+89.00
5120	-5.0	-.1000	.0119	-.0881	+81.16

Table XI.

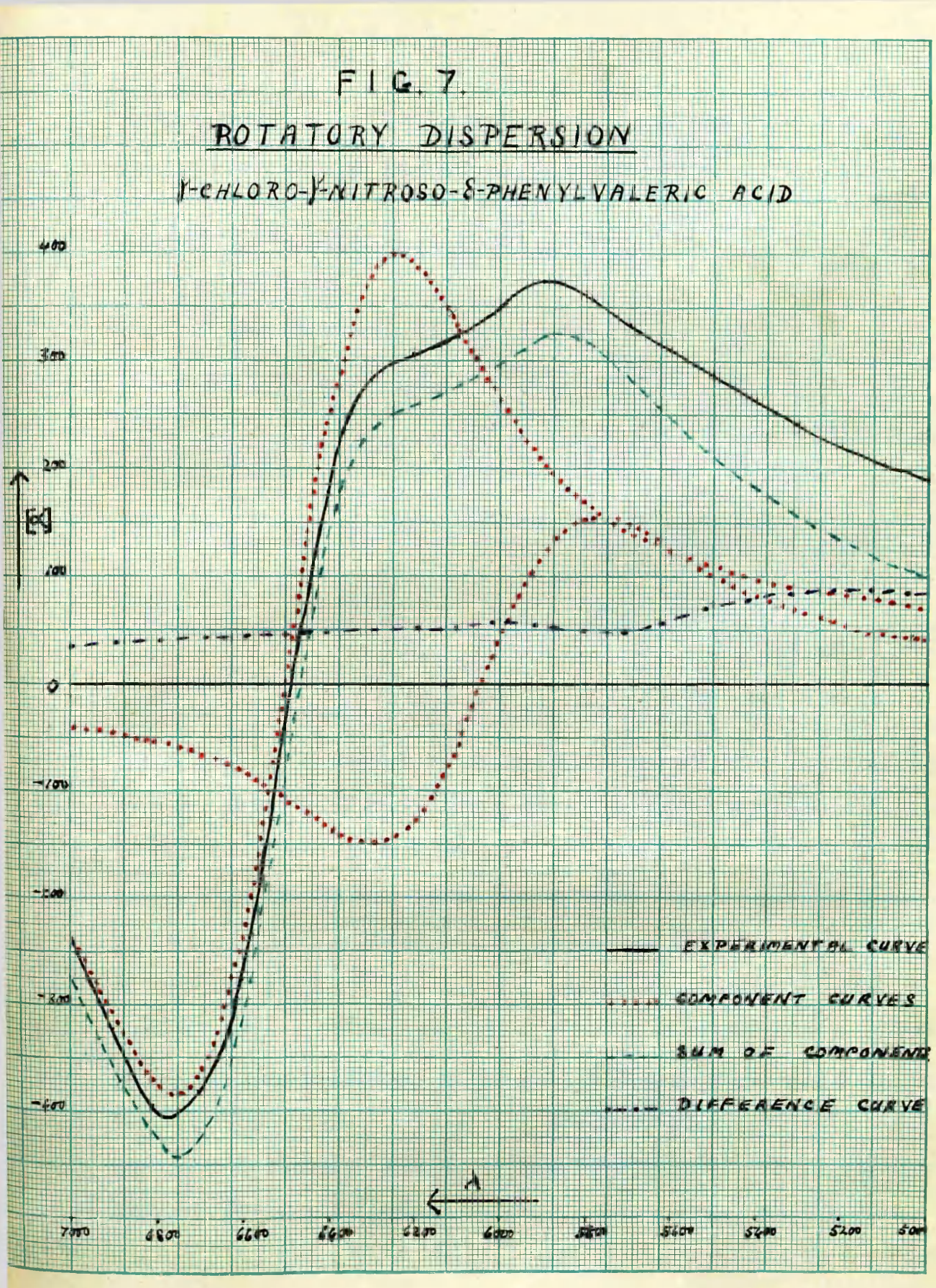
Partial Rotations calculated from Small Component Curve of Circular Dichroism.

λ	c	$e^{-c^2}\int_0^c e^{x^2}dx$	$\frac{\theta}{2(\lambda+\lambda_0)}$	m	$[\alpha]$
6847	2.8	.1936	.0112	.2048	-51.21
6731	2.4	.2353	.0113	.2466	-62.72
6616	2.0	.3013	.0114	.3127	-80.93
6501	1.6	.4000	.0115	.4115	-108.3
6386	1.2	.5073	.0116	.5189	-139.1
6270	.8	.5321	.0117	.5438	-148.5
6155	.4	.3594	.0118	.3712	-103.2
6040	0	.0000	.0119	.0119	- 3.4
5925	- .4	-.3594	.0120	-.3474	+100.3
5810	- .8	-.5321	.0122	-.5199	+153.2
5695	-1.2	-.5073	.0123	-.4950	-148.8
5579	-1.6	-.4000	.0124	-.3876	-119.0
5464	-2.0	-.3013	.0125	-.2888	90.48
5349	-2.4	-.2353	.0127	-.2227	71.29
5234	-2.8	-.1936	.0128	-.1808	59.14
5032	-3.5	-.1429	.0130	-.1299	44.20

FIG. 7.

ROTATORY DISPERSION

1-CHLORO-1-NITROSO-2-PHENYLVALERIC ACID



Experimental: (A) Preparation of menthyl and bornyl esters of chloronitroso acids.

Attempted preparation of l-menthyl β-chloro-β-nitroso-γγ-dimethylvalerate.

The synthesis may be summarised as follows:-

$$CH_3CO\,CH_3 \longrightarrow (CH_3)_3\cdot C\cdot CO\,CH_3 \xrightarrow{Br_2} (CH_3)_3C\cdot COCH_2\cdot Br$$

$$\xrightarrow{KCN} (CH_3)_3C\cdot CO\,CH_2\cdot CN \xrightarrow[HCl]{EtOH} (CH_3)_3C\cdot CO\cdot CH_2\cdot C(=NH\cdot HCl)(OEt)$$

$$\xrightarrow{H_2O} (CH_3)_3C\cdot CO\,CH_2\cdot CO_2Et \xrightarrow{l\text{-menthol}} (CH_3)_3C\cdot CO\,CH_2\cdot CO_2C_{10}H_{19}$$

$$\xrightarrow{NH_2OH} (CH_3)_3C\cdot C(=NOH)\cdot CH_2\cdot COOC_{10}H_{19} \xrightarrow{Cl_2} (CH_3)_3C\cdot C(NO)(Cl) - CH_2\cdot COOC_{10}H_{19}$$

Stage I. Pinacolone was prepared from acetone[53].

Stage II. Bromination of the pinacolone in chloroform solution at 0°C with vigorous stirring gave ω-bromo pinacolone in 60% yield[64]. B.P. 74-76°C/12 mm.

Stage III. The latter compound was treated in aqueous alcoholic solution with two molecules of potassium cyanide to give ω-cyanopinacolone[65], which was purified by steam distillation. M.P. 67-68°C. (Yield, 40%).

Stage IV. To a mixture of 10 gms. ω-cyano pinacolone (dried in a vacuum desiccator), 7 ccs. absolute alcohol and 70 ccs. sodium dried ether, cooled in ice, dry hydrogen chloride was added until the solution was saturated. After leaving over-

night the ether was removed leaving the solid acetimino ether hydrochloride which was not purified for the next stage. Yield = 85%.

Stage V. The latter compound was dissolved in water and heated for 2 hours on a water bath at 60°C giving tert. valeryl ethyl acetate in 70% yield[66]. B.P. 96-98°C/18 mm.

Stage VI. By heating 10 gms. of the ethyl ester with 9.1 gms. l-menthol for 5 hours on an oil bath at 160-170°C, and fractionating the mixture under reduced pressure, the menthyl ester was obtained in 50% yield. B.P. 138-142°C/0.8 mm.

Stage VII. Attempts to prepare the oxime and chloronitroso compound.

a). An alcoholic solution of the menthyl ester was refluxed for two hours with an aqueous alcoholic solution of hydroxylamine. The mixture was poured into water and extracted with ether. After drying the ether solution over sodium sulphate, it was treated with chlorine, when a pale blue colour was obtained. Removal of the ether gave a blue oil which did not solidify on cooling and soon turned green.

b). The above method was repeated, but this time the ether solution, after drying over sodium sulphate, was evaporated leaving an oil from which a white solid crystallised. This solid was crystallised from alcohol and melted at 105°C. On dissolving it in sodium dried ether and passing in chlorine no blue colour was obtained indicating that it was not the

oxime. When the oily filtrate was dissolved in dry ether and the solution treated with chlorine, a pale blue colour was obtained, but evaporation of the ether again only gave a little blue oil.

c). No heating was applied this time in the preparation of the oxime but again only a small amount of blue oil was obtained on treatment with chlorine.

An examination was made of the white solid produced in attempt (b). (Found: C, 59.6; H, 7.4; N, 9.9; M, 137. The isoxazolone compound from tert. valeryl acetic acid of formula $C_7H_{11}O_2N$ requires: C, 59.6; H, 7.8; N, 9.9%; M,141). These results indicate that in the preparation of the oxime of the menthyl ester, menthol is hydrolysed off, and the oxime of the acid ring closes to give the isoxazolone compound. The appearance of a faint blue colour on treatment with chlorine is due to the presence of a small amount of oxime, probably of the acid, in the ether solution.

Preparation of l-menthyl γ-chloro-γ-nitrosovalerate.

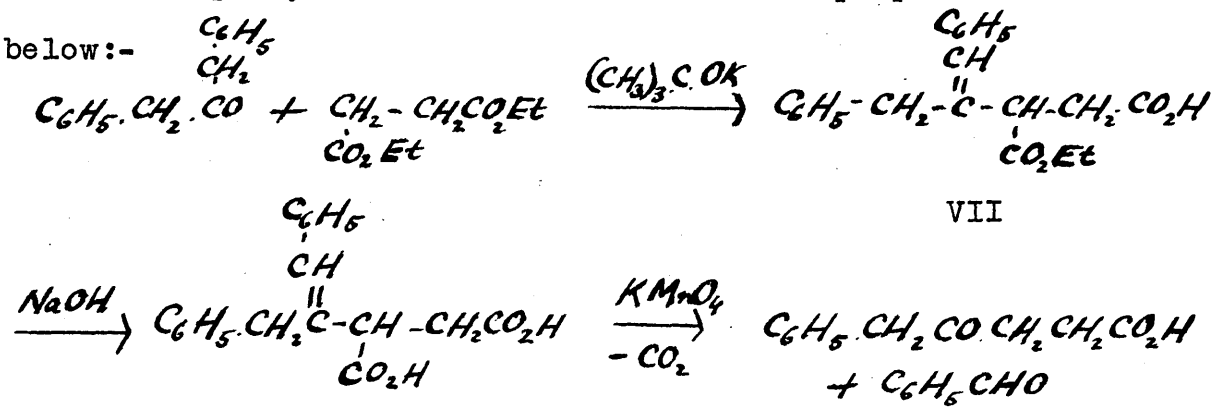
Menthyl laevulinate was first prepared[67], and from it the oxime in the usual manner. The latter, being a white solid, was crystallised from alcohol, m.p. 54-56°C, and thoroughly dried in a vacuum desiccator. It was then dissolved in sodium dried ether and treated with chlorine until the solution was green. After removing the ether, a blue oil was obtained which did not solidify.

Preparation of l-bornyl-γ-chloro-γ-nitrosovalerate.

Bornyl laevulinate was prepared in the same way as described for the menthyl ester using l-borneol instead of l-menthol. In this case the oxime was an oil, which again gave a liquid chloronitroso compound.

Preparation of l-menthyl-γ-chloro-γ-nitroso-δ-phenylvalerate.

δ-phenyl laevulinic acid was first prepared as outlined below:-



VII

1). Condensation of dibenzyl ketone and diethyl succinate.

The method described in the literature[68] in which the condensation was effected in the presence of sodium ethoxide in dry ether, leaving for several weeks, was not attempted. Instead the condensation was carried out in presence of potassium tert. butoxide as follows[69]:-

A mixture of 105 gms. dibenzyl ketone (.5 moles), 130 gms. diethyl succinate (.75 moles) and 100 ccs. tert. butyl alcohol (to aid in the transfer), was added to a solution of 21.5 gms. potassium (.55 moles) in 400 ccs. tert. butyl alcohol, and the mixture refluxed for 6 hours in a nitrogen atmosphere.

After cooling, the brownish coloured solution was acidified with dilute hydrochloric acid and the solvent removed under reduced pressure. The semi-solid residue was taken up in ether and the ether layer thoroughly extracted with sodium bicarbonate solution, the aqueous layers being combined and acidified. A pink oil separated which soon solidified, and after washing with ether, was crystallised from alcohol. M.P. 128°C. (Found: C, 74.8; H, 7.0. Calculated for the half ester, VII, of formula $C_{21}H_{22}O_4$: C, 74.6; H, 6.5%). (Yield, 28%).

2). Hydrolysis of VII to the di-acid.

The half ester (53 gms.) was boiled for 2 hours with a solution containing 18 gms. sodium hydroxide in 360 ccs. water, and after cooling, the solution was acidified. The colourless oil which separated, soon crystallised to a white solid. M.P. 148°C. (Yield, theoretical).

3). Oxidation of the di-acid to δ -phenyl laevulinic acid[70].

40 gms. of the di-acid were dissolved in an alkaline solution containing 22 gms. (1½ moles) of anhydrous sodium carbonate. To this solution, kept at 0°C by immersion in a freezing mixture, was slowly added (over the space of one hour) with stirring 700 ccs. of a 4% solution of potassium permanganate. After the addition of the first few drops the odour of benzaldehyde was perceptible. When all the permanganate solution had been added, the manganese dioxide precipitate was filtered, and the filtrate extracted three times with ether to remove the benzaldehyde.

The solution, after acidification and one extraction with ether, was placed in a continuous ether extractor for 6 hours. Evaporation of the combined ether extracts gave a yellow oil, which, with an aqueous alcoholic solution of semicarbazide, gave 26 gms. of the semicarbazone of δ -phenyl laevulinic acid, m.p. 182°C. To regenerate the keto acid from the semicarbazone, the latter was warmed on the water bath with 18% sulphuric acid. On cooling, the oil which had separated, solidified, and by crystallising the solid from 40-60 petroleum ether, pure white needles of δ -phenyl laevulinic acid were obtained. M.P. 53-55°C. (Yield, 40%).

Preparation of l-menthyl δ -phenyl laevulinate.

The menthyl ester was prepared by heating 8 gms. of the acid with 15.4 gms. of l-menthol on an oil bath at 95-105°C for 20 hours, dry hydrogen chloride being frequently passed into the liquid. The cooled mixture was dissolved in ether, washed with water and sodium bicarbonate solution, and dried over potassium carbonate. After evaporating the ether and removing the menthol under reduced pressure, the residue was cooled in ice. White crystals were deposited, which, after crystallisation from alcohol, melted at 31°C. (Found: C, 76.7; H, 8.9. $C_{21}H_{30}O_3$ requires: C, 76.4; H, 9.1%).

The oxime was prepared in the usual way and crystallised from 40-60 petroleum ether. M.P. 76°C. (Found: C, 73.2; H, 8.8; N, 4.2. $C_{21}H_{31}O_3N$ requires: C, 73.1; H, 9.0; N, 4.1%).

Treatment of the oxime in dry ether with chlorine gave a liquid chloronitroso compound, which did not solidify.

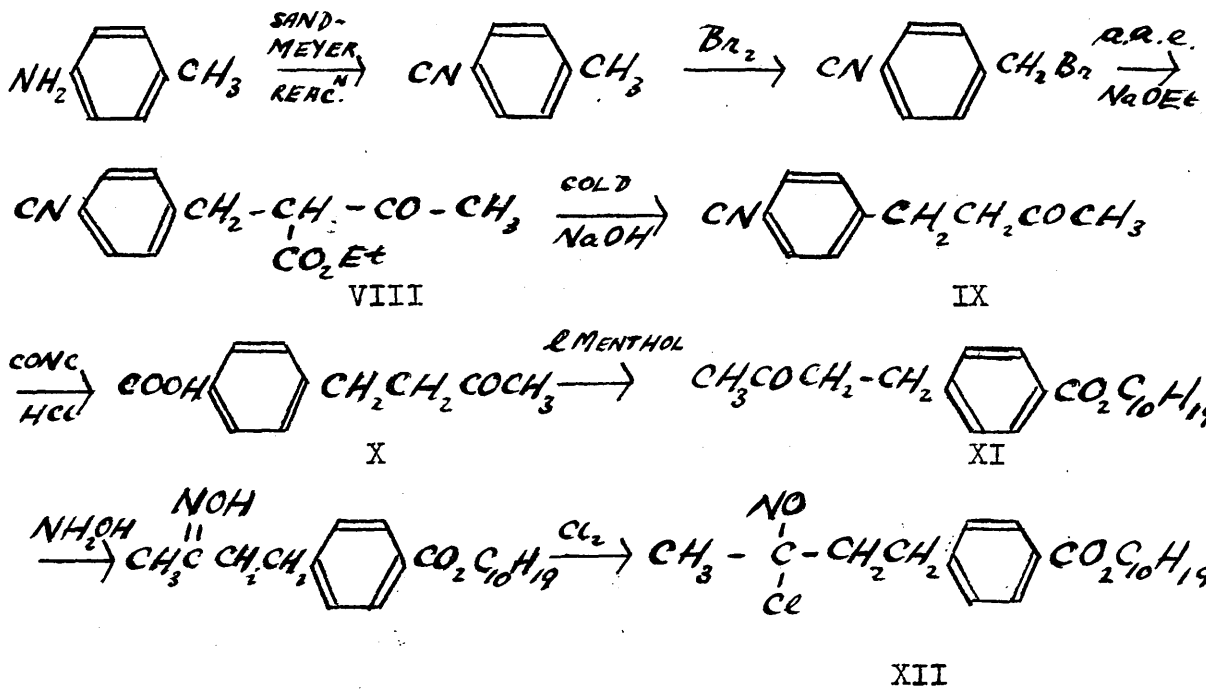
Preparation of l-bornyl γ-chloro- γ-nitroso- δ-phenylvalerate.

l-Bornyl δ-phenyl laevulinate was prepared in the same way as the menthyl ester, but being an oil, it was purified by distillation. B.P. 208°C/1.5 mm. A semicarbazone was prepared, which, after crystallisation from alcohol, melted at 148°C. (Found: C, 68.4; H, 7.9; N, 11.1. $C_{22}H_{31}O_3N_3$ requires C, 68.6; H, 8.1; N, 10.9%).

The oxime was an oil, as was also the chloronitroso compound prepared from it.

Preparation of the menthyl ester of γ-chloro- γ-nitroso- α-(p-carboxyphenyl) butane.

The synthesis may be summarised as follows:-



Stage I. p-Tolunitrile was prepared from p-toluidine[71].

Stage II. Bromination of the latter[72] at 200°C gave p-cyano benzyl bromide in 45% yield. M.P. 115°C.

Stage III. Condensation with ethyl acetoacetate.

To an alcoholic solution of sodium ethoxide (containing 4 gms. sodium in 50 ccs. alcohol) were added 44 gms. ethyl acetoacetate and 28 gms. p-cyano benzyl bromide. The mixture was shaken for a few minutes, whereupon considerable heat developed and a precipitate of sodium bromide was formed. After refluxing the mixture for 2 hours, the alcohol was removed and the residue extracted with ether and dried over sodium sulphate. The ether was evaporated, and the remaining liquid distilled under reduced pressure to remove the excess ethyl acetoacetate. Thereafter the product was distilled under high vac. B.P. 180°/1.5 mm. (Yield, 60%).

Stage IV. Hydrolysis of the condensation product.

The substance VIII can hydrolyse in two ways, either giving the acidic product, p-cyano hydrocinnamic acid, $CN\,C_6H_4 \cdot CH_2 \cdot CH_2 \cdot COOH$, XIII, or the ketonic product IX, the latter being the one desired. Some difficulty was encountered in the hydrolysis, owing to the tendency of the former compound to be produced. Three methods were tried:-

a). Hydrolysis with acid. It was thought that by using acid, not only would IX be formed, but also the cyano group would be hydrolysed giving X in one step. By boiling with 50% sulphuric

acid for 2 hours, a white solid (m.p. 284°C) separated which was acidic but not ketonic - probably p -carboxyl hydrocinnamic acid, COOH $C_6H_4CH_2CH_2COOH$. It was purified from glacial acetic acid. (Found: C, 61.7; H, 5.2. Calc. for $C_{10}H_{10}O_4$: C, 61.9; H, 5.2%).

b). In the second attempt, a method described[73] for a compound similar to VIII (but with no p -cyano group) was carried out. The ester VIII was heated on the steam bath for 2 hours with 10% alcoholic potassium hydroxide solution, when a solid potassium salt separated. After removing the alcohol, hydrochloric acid was added giving a white solid which was acidic but not ketonic and contained nitrogen - probably XIII. It was purified from alcohol, m.p. 134°C. (Found: C, 68.7; H, 5.4; N, 8.3. Calc. for XIII of formula $C_{10}H_9O_2N$: C, 68.6; H, 5.1; N, 8.0%). Thus again the hydrolysis resulted in the production of the acidic product.

c). This time heating was avoided during the hydrolysis. The ester was allowed to stand for 4 hours in the cold with 5% sodium hydroxide solution (in which it soon dissolved). After acidifying, the solution was boiled, when carbon dioxide, from the unstable β -keto acid, was evolved, and an oil separated which was extracted with ether. Some of the cyano acid XIII was formed, but was easily removed from the ether solution with sodium bicarbonate solution. Removal of the ether gave a ketone containing nitrogen, probably IX (m.p. 55°C). After

boiling for 3 hours with concentrated hydrochloric acid, the ketonic acid X crystallised out on cooling and was purified from alcohol, m.p. 124°C. (Found: C, 69.1; H, 5.9. X of formula $C_{11}H_{12}O_3$ requires: C, 68.8; H, 6.2%). (Yield, 25%).

Stage V. Preparation of the menthyl ester.

The method was the same as that described for l-menthyl δ-phenyl laevulinate. As the ester in this case was an oil it was purified by distillation. B.P. 210°C/1 mm. A semicarbazone was prepared and purified from alcohol. M.P. 168°C. (Found: C, 68.1; H, 8.3; N, 10.6. $C_{22}H_{33}O_3N_3$ requires: C, 68.2; H, 8.5; N, 10.9%).

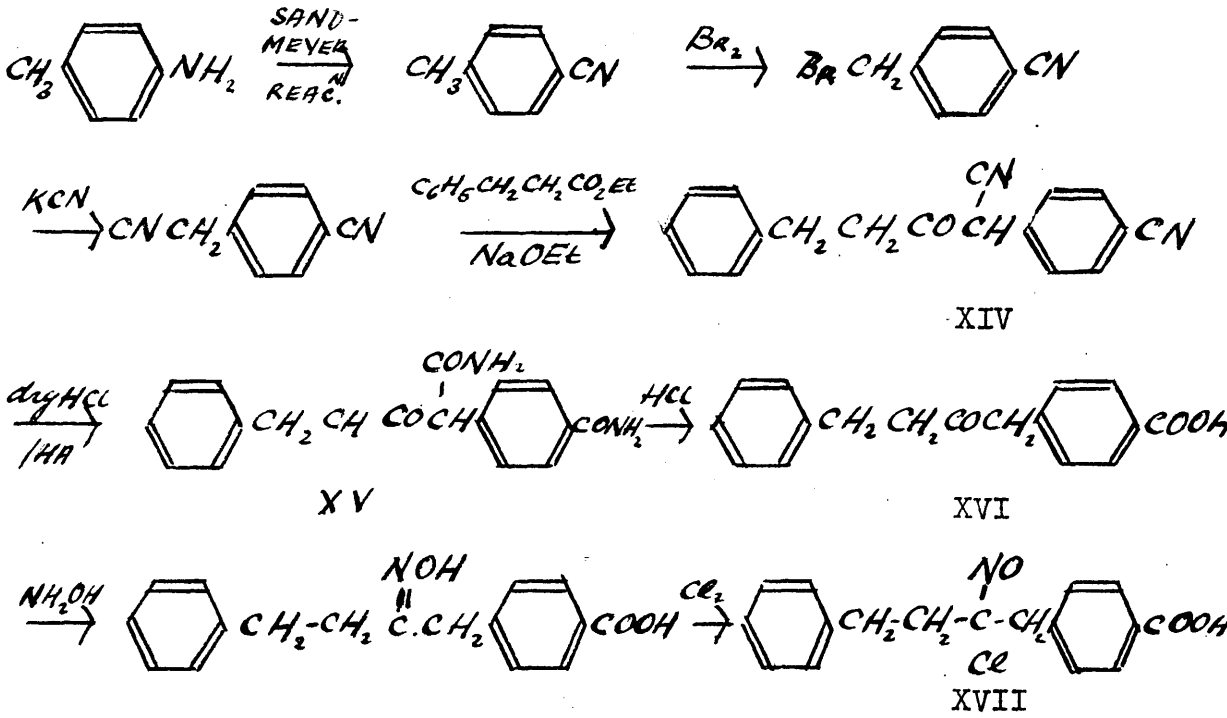
Stage VI. Preparation of oxime and chloronitroso compound.

The oxime was prepared in the usual way, but being an oil, could not be purified. It was therefore dried thoroughly, dissolved in dry ether and treated with chlorine in the usual manner. After evaporating the ether, a viscous blue oil remained which solidified on cooling. It was purified from alcohol. M.P. 44-48°C. (Found: C, 66.6; H, 7.9; N, 3.5. $C_{21}H_{30}O_3N\,Cl$ requires: C, 66.4; H, 7.9; N, 3.7%).

(B). Preparation of Chloronitroso Acids.

Preparation of β-chloro-β-nitroso-α-(p-carboxyphenyl)-δ-phenylbutane.

The synthesis which was carried out may be summarised as follows:-



Stage I. p-Tolunitrile was prepared from p-toluidine[71].

Stage II. Bromination of the latter[72] at 200°C gave p-cyano benzyl bromide.

Stage III. Preparation of p-cyano benzyl cyanide.

To 54 gms. of the bromo compound in 300 ccs. alcohol, 21 gms. of analar potassium cyanide, dissolved in the smallest volume of water, was added, and the mixture refluxed gently for an hour. Most of the alcohol was removed under reduced pressure, and the pink solid which separated was filtered, washed well with water to remove the potassium bromide, and crystallised from alcohol. M.P. 100°C. (Yield, 50%).

Stage IV. Condensation of p-cyano benzyl cyanide with dihydro ethyl cinnamate.

The dihydro ethyl cinnamate was first prepared as follows:-

150 gms. ethyl cinnamate dissolved in 300 ccs. alcohol, and 5 gms. of copper chromite catalyst were introduced into the steel bomb of the hydrogenation apparatus, and the temperature raised to 179°C, and the pressure to 95 atmospheres. After one hour under these conditions the reaction was complete. The copper chromite was filtered off and the product distilled. B.P. 121°C/10 mm. (Yield, 90%).

Condensation. A mixture of 6.2 gms. of the cyanide and 7.8 gms. of the ester was added to a solution of sodium ethoxide in alcohol (prepared by dissolving 1 gm. of sodium in 14 ccs. of alcohol). The solution turned deep red and after a short time of refluxing, the mixture became almost solid. Refluxing was continued for 5 hours after which 100 ccs. of 1% sodium hydroxide solution were added, but very little of the solid appeared to dissolve. The solution was filtered and the reddish brown filtrate acidified, when a yellow oil separated which was extracted with ether. Evaporation of the ether gave 1.5 gms. of a yellow solid which was purified from methyl alcohol. M.P. 125°C. (Yield, 12%). (Found: C, 78.8; H, 5.2; N, 10.3. XIV of formula $C_{18}H_{14}ON_2$ requires: C, 78.8; H, 5.1; N, 10.2%). Thus a small amount of the required condensation product has been obtained.

In order to improve the yield, the following variations from the above method were tried:-

a). The condensation was carried out in benzene solution using sodium methoxide as condensing agent, but the yield was considerably lower than before.

b). To the sodium ethoxide in alcohol, the reagents were added and the mixture allowed to stand at room temperature for 48 hours. None of the condensation product was obtained in this case.

c). The first method using sodium ethoxide in alcohol was repeated, the time of refluxing being reduced to 2 hours without any improvement in the yield being obtained.

d). The time of refluxing was increased to 10 hours without any increase in the yield.

e). Since p-cyano benzyl cyanide was much more soluble in dioxan than in alcohol, the reagents were dissolved in this solvent before adding to the alcoholic sodium ethoxide solution. Again the yield was very poor.

In every method attempted so far, the dark red mixture, after refluxing, was mostly insoluble in dilute sodium hydroxide, and was resin-like in appearance. Owing to the several active groups in the reagents, it is possible that other condensations occur, perhaps forming long chained molecules, thereby accounting for the very poor yield of the desired product. Since the first method gave the best yield, this was the one adopted, and from 74 gms. of p-cyano benzyl cyanide, 17 gms. of XIV were obtained.

Stage V. Hydrolysis of the cyanide to the amide.

Into a solution of XIV in glacial acetic acid (kept at 0°C in an ice bath), dry hydrogen chloride was bubbled in until the solution was saturated. After allowing to stand for 40 hours most of the solvent was removed under reduced pressure. On adding water to the residue a buff coloured solid separated. A small portion was purified from alcohol in which it was only sparingly soluble. M.P. 219°C. (Found: C, 69.5; H, 5.6; N, 8.9: XV of formula $C_{18}H_{18}O_3N_2$ requires: C, 69.7; H, 5.8; N, 9.0%). The main portion was used directly for the next stage without purification.

Stage VI. Hydrolysis to the keto acid.

The amide was boiled for 12 hours with concentrated hydrochloric acid, the solid filtered, and dissolved as far as possible in dilute sodium hydroxide solution. Acidification of the latter gave a white solid which was crystallised twice from alcohol. M.P. 148°C. (Found: C, 76.0; H, 6.0. XVI of formula $C_{17}H_{16}O_3$ requires: C, 76.1; H, 6.0%). Only 2.7 gms. of XVI were obtained.

Stages VII and VIII. Preparation of oxime and chloronitroso acid.

Since the oxime (prepared in the usual manner) was a low melting solid, it was treated directly in dry ether solution with chlorine. Removal of the ether gave a blue solid which was purified from methyl alcohol. M.P. 158°C (with

decomposition). (Found: C, 64.6; H, 4.9; N, 4.5. XVII of formula $C_{17}H_{16}O_3NCl$ requires: C, 64.2; H, 5.0; N, 4.4%). Yield = 1.9 gms.

Preparation of γ-chloro-γ-nitroso valeric acid.

When equivalent amounts of hydroxylamine hydrochloride and potassium acetate in water were added to an aqueous solution of laevulinic acid, and the mixture allowed to stand for 3 hours, a white solid separated which was purified from alcohol. M.P. 94-96°C. (Yield, 70%).

Into a solution of the oxime in sodium dried ether, chlorine was passed until the solution was green in colour. Evaporation of the ether gave a deep blue solid, which was dissolved in n-hexane at room temperature. When the latter solution was concentrated under reduced pressure, the chloronitroso acid crystallised out in blue plates. M.P. 33°C. (Yield, 65%).

Preparation of γ-chloro-γ-nitroso-δ-phenylvaleric acid.

1). δ-Phenyl laevulinic acid was synthesised as described previously.

2). The oxime which was prepared in the same way as described for laevulinic acid oxime, was washed with water and dried thoroughly in a vacuum desiccator. M.P. 98-100°C. (Yield, 90%).

3). A solution of the oxime in sodium dried ether was treated with chlorine in the usual manner. The blue solid obtained after removal of the ether was dissolved in n-hexane (with slight warming) and after cooling the solution in the

refrigerator blue crystals of the chloronitroso acid were obtained. M.P. 72°C. (Yield, 65%). (Found: C, 54.7; H, 5.1; N, 6.0. $C_{11}H_{12}O_3NCl$ requires: C, 54.7; H, 5.0; N, 5.8%).

(C). Preparation[74] and Resolution of β-naphthol phenylaminomethane.

For the resolution of the base, a method similar to that described by Betti[75] was followed. 44 gms. of the base were dissolved in 1400 ccs. 95% alcohol avoiding warming above 50-60°C, and to the almost colourless solution, 26.8 gms. d-tartaric acid in 80 ccs. alcohol were added. Almost immediately, small shining crystals commenced to be deposited, and after two hours were filtered off and washed several times with boiling alcohol. The total yield obtained after the washings was almost 35 gms. (i.e., approximately 50%).

To recover the free base, the tartrate was ground finely with a little water to form a smooth paste and treated with a 20% sodium hydroxide solution with stirring at 0-5°C. When the solution was strongly alkaline, it was extracted repeatedly with ether, the combined extracts being dried over sodium sulphate. The solution was then boiled with animal charcoal, filtered and concentrated to small volume. On cooling pure, white, silky needles of the d-base were obtained. M.P. 136°C. $[\alpha]_D$ = +57°. (Yield, 55%).

Summary.

In Part I of this thesis I have described the preparation of the following chloronitroso compounds:-

(A). β-chloro-β-nitroso-$\gamma\gamma$-dimethylbutane, $CH_3 \cdot CCl(NO) \cdot CMe_3$.

(B). β-chloro-β-nitroso-$\delta\delta$-dimethylpentane, $CH_3 \cdot CCl(NO) \cdot CH_2 \cdot CMe_3$.

(C). γ-chloro-γ-nitroso-$\beta\beta$-dimethylpentane, $CH_3 \cdot CH_2 \cdot CCl(NO) \cdot CMe_3$.

(D). β-chloro-β-nitrosohexane, $CH_3 \cdot CCl(NO) \cdot (CH_2)_3 \cdot CH_3$.

Of these, (B) and (C) are new substances, but being non-distillable blue oils, they were not investigated further.

The products of photochemical decomposition of (A) have been investigated in various solvents, and the reaction mechanisms discussed. In methyl and ethyl alcohols (which can supply hydrogen atoms) the main products were, a) hydrogen chloride, b) the oxime of pinacolone, and c) formaldehyde or acetaldehyde, depending on whether methyl or ethyl alcohol was used as solvent. A rearrangement appears to take place in other solvents (such as carbon tetrachloride, benzene and ether).

Asymmetric photochemical experiments were also carried out with (A) taking the decomposition in stages to 94%. Polarimetric examination of the recovered material which had been exposed to right-handed and left-handed circularly polarised light, respectively, gave the values $[\alpha]^{18^\circ}_{5200} = -3.5^\circ$ and $+3.6^\circ$.

Similar experiments with (D) taking the decomposition to 96% gave the results $[\alpha]^{18^\circ}_{520m}$ = -1.67° and +1.67°. Partial resolutions of (A) and (D) have thus been achieved with circularly polarised light.

In Part II, the preparation of four menthyl and two bornyl esters of chloronitroso acids is described. Only one of these, viz., $CH_3 \cdot CCl(NO) \cdot CH_2 \cdot CH_2 \cdot C_6H_4 \cdot COOC_{10}H_{19}$, was crystalline, the others being viscous blue oils, unsuitable for resolution purposes. Attempts were made to resolve the solid menthyl ester by crystallisation from various solvents, but no change in either the melting point or the specific rotation was produced.

With resolution still in view, three chloronitroso acids were then synthesised:-

(I) β-chloro-β-nitroso-α-(p-carboxyphenyl)-δ-phenylbutane
$C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CCl(NO) \cdot CH_2 \cdot C_6H_4 \cdot COOH$.

(II) γ-chloro-γ-nitrosovaleric acid,
$CH_3 \cdot CCl(NO) \cdot CH_2 \cdot CH_2 \cdot COOH$.

(III) γ-chloro-γ-nitroso-δ-phenylvaleric acid,
$C_6H_5 \cdot CH_2 \cdot CCl(NO) \cdot CH_2 \cdot CH_2 \cdot COOH$.

All these are blue crystalline solids, and (I) and (III) are new substances. The synthesis of (I) required eight stages of which the last five were new.

An unstable quinine salt was formed by (I) in ether solution, but crystallisation of this salt from methyl acetate

failed to resolve the acid. Owing to the great difficulty of preparation and the small yields of the acid obtained, further investigations were not undertaken.

Attempts were then made to resolve (II) with quinine. After six crystallisations of the quinine salt from ethyl alcohol, the specific rotation had decreased from $[\alpha]^{18°}_{5700} = -136°$ to $[\alpha]^{18°}_{5700} = -120°$, and polarimetric examination of the recovered acid gave the value $[\alpha]^{18°}_{5700} = +16°$ ($l = 1$, c = 1% in alcohol). As the progress of the resolution appeared to be very slow, more of the quinine salt was prepared and crystallised eight times from methyl acetate. Again the decrease in the specific rotation was very slow. After the eighth crystallisation $[\alpha]^{18°}_{5700}$ was $-116.5°$, but had not reached a constant value. The recovered acid exhibited the Cotton effect in the region of absorption, the maximum specific rotation being $+30°$ at 6100 A.

A salt of (II) was then formed with d-β-naphthol phenylaminomethane, but three crystallisations from ethyl acetate produced very little change in the specific rotation. The salt was extremely unstable.

More encouraging results were obtained with (III). Although this acid formed only sticky blue oils with the common alkaloid bases, a pale blue salt was readily obtained with d-β-naphthol phenylaminomethane, which crystallised well from ethyl acetate. After ten crystallisations from this solvent, the specific rotation had increased from $[\alpha]^{18°}_{5600} = +38.4°$ to

$[\alpha]_{5600}^{18^\circ} = +110.6^\circ$. The rotatory dispersion and circular dichroism of the recovered acid were examined in the region of absorption. The former reached $+372^\circ$ at 5900 A and decreased through zero at approximately 6500 A to -394° at 6800 A. This is the first satisfactory resolution of a chloronitroso acid.

The absorption spectrum (which was measured photographically by means of a Hilger Spekker Photometer in conjunction with a glass spectrograph), showed a characteristic band in the red due to the nitroso group. A curve of composite form was also obtained when circular dichroism was plotted against wave-length. An analysis of these two curves was then carried out, the former being represented as the sum of three normal frequency curves, and the latter as the sum of two. Using Lowry and Hudson's modification of Kuhn's equation, partial rotations were calculated for each of the circular dichroism components. When the sum of these was subtracted from the experimental rotatory dispersion curve, a fairly smooth difference curve was obtained. Thus the contribution to the rotatory dispersion due to the nitroso group has been successfully eliminated.

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